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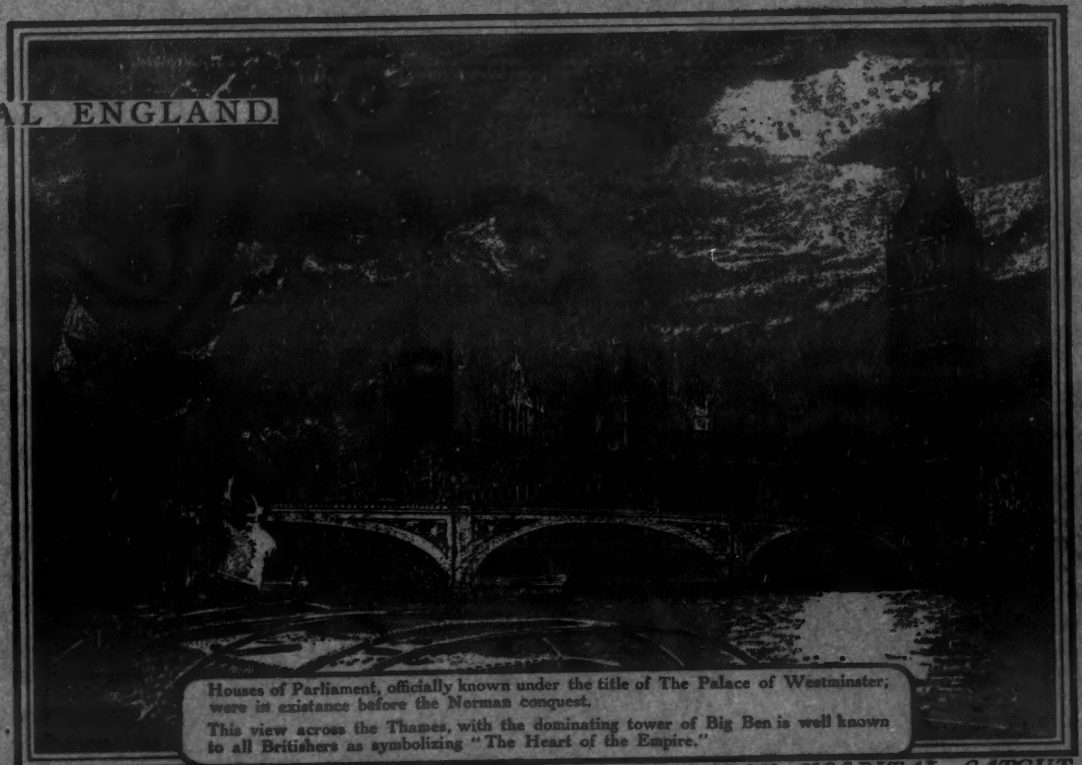

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The Journal of
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VOL. 49, No. 4 NEW SERIES AUGUST, 1942

A Clinical Study of Menstruation with Special Reference to Primary Dysmenorrhoea

BY

HELEN M. TAYLOR, M.D. (Aber.), M.M.S.A. (Lond.)

INTRODUCTION

RECENT advances in our knowledge of the action of the pituitary and ovarian hormones have thrown a new light on the function of menstruation. There is still, however, a difference of opinion among gynaecologists as to the significance of menstrual irregularities in patients who have no sign of pelvic disease, and even more disagreement concerning the significance of the mental and physical lassitude, abdominal pain and discomfort, and other symptoms of which so many women complain about the time of their periods. Some are inclined to think that the lesser degrees of pain and functional depression must be regarded as physiological. Others, basing their arguments on the admitted freedom of some women from all such symptoms, will not accept this. All agree that an incapacitating degree of dysmenorrhoea is abnormal, but an explanation of the cause of such pain is not universally approved. Dysmenorrhoea has been cured by the most diverse methods, but not one is consistently successful.

This investigation was begun because I was very dissatisfied with the results of the treatment of dysmenorrhoea among my own patients. I determined to see whether a clinical record of their general health and environment, together with an inquiry into the chief features of menstruation in a group of young women, would help towards a better understanding of the problem. National Health Insurance practice, in which the fee difficulty does not arise, and which affords frequent opportuni-

ties to watch the progress of individual patients, seemed to offer a good field for such a study.

Choice of Patients and Scope of the Investigation.

In order to eliminate symptoms which might have had their origin in the traumata or infections caused by abortion or childbirth, patients who had been pregnant were not included in the investigation. Women at or about the age of the menopause were also excluded. On the other hand, I tried to include all those patients who were still on my National Health Insurance list, and some private patients who had at one time or another sought treatment for dysmenorrhoea. Further limitation was not made in the choice of cases; patients were approached, as opportunity arose during the routine work of the practice, whether or not they suffered from dysmenorrhoea. A convenient appointment was made for each patient. The examination consisted of a general physical overhaul—height, weight, nutrition, haemoglobin, heart, lungs, abdomen, urine, special senses and (in most cases) pelvic organs, along with detailed questions about the menstrual history and symptoms. Notes were also made of employment, home circumstances, recreation and temperament, and each patient was asked to keep an accurate record of her diet during one week. The interview lasted, on an average, about one and a half hours. The information thus gained was supplemented by my previous knowledge of the patient and my record of her clinical history. I had been the medical attendant of most of the patients for a number of years before the investigation began, the maximum being 11 years, the average over the whole series $5\frac{1}{2}$ years. I hoped this might offset to some extent the disadvantage of a study depending so much on question and answer.

In all 200 patients were examined, 189 of whom came under the National Health Insurance Scheme. The youngest was $15\frac{1}{2}$, and the eldest 38 years of age. Twenty-five were under 18, 125 between 18 and 25, and 50 over 25 years. Eighty-four were employed in offices, 78 worked in factories, 19 were shop assistants, 12 were engaged in domestic work, 6 in professional work, and one was still at school. Twelve were married.

Menstruation

Age of onset. Menstruation began between 12 and 15 years in 83 per cent of the group. One girl had had regular periods since $10\frac{1}{2}$ years, dysmenorrhoea beginning when she was 16

years of age. Another girl did not begin to menstruate until she was 19 but was regular thereafter. Dysmenorrhoea began with her first period. Sixty-one girls stated that menstruation recurred regularly to the day (generally 28 days' interval, sometimes 24, 26 or 30 days' interval); 114 stated that it recurred with monthly regularity to within a few days; while in 25 the intervals between the periods were stated to vary frequently by more than one week. Calendar records were kept by 30 girls at my request for 8 to 12 months. On analysis none of these showed absolutely regular menstruation though 7 of the girls who kept records had stated their periods were "regular to the day." In 25 the interval varied by a few days only. In the remaining 5 it fairly often varied by more than a week (as the girls had themselves reported). The records bore out the statements made by many of the patients that the monthly rhythm was often upset when they went on holiday.

Eighteen girls gave a history of menstruation having been grossly irregular for some months after the *ménarche*; in 3 it remained irregular. Twenty-six in whom it was regular at the time of examination said that menstruation had been irregular (i.e. more than one week's variation in the intermenstrual periods) at some time in their experience. Eight gave a history of having had excessive and too frequent periods at some time.

One patient with grossly irregular menstruation developed clinical signs of pulmonary tuberculosis while under observation. Another with a gastric ulcer, in whom the haemoglobin fell to 48 per cent, had no irregularity or obvious alteration in the duration of menstruation, or in the amount of blood lost throughout her illness. Many histories could be quoted which suggest the influence of emotional factors on menstruation. For example, one woman had her periods at 6- to 8-weekly intervals from the age of 14 until she married at 26. After marriage she menstruated regularly every 28 days. Another had very irregular periods (2- to 8-monthly intervals) from 14 until 20 years of age, when she sought advice because she was "walking out" and was anxious about her ability to have children. She also complained of dysmenorrhoea. On examination a small round acutely ante-flexed and ante-verted uterus was found. Treatment was not given beyond reassurance and an explanation of the physiology of menstruation, emphasis being laid on the fact that the patient had menstruated, though irregularly. Within the next 8 months menstruation occurred three times, then it appeared regularly every month. When last seen 2 years later,

it had continued regular, and she said she had not had any dysmenorrhoea at all since her examination.

Duration and amount of menstrual loss. Twenty-eight girls stated that menstruation generally lasted for less than 4 days; in 101 it was said to last between 4 and 5 days, and in 71 for over 5 days. Unfortunately little reliance can be placed on a woman's own estimate of the amount of blood lost. In the present series 27 considered the loss to be scanty, 123 thought that it was about average and 50 that it was profuse.

Menstrual hygiene. Only 17 of the 200 patients ever bathed during menstruation, and some of these only did so towards the end of their periods. Many of these girls, however, came from homes which had no bathroom, and a weekly bath was all that was customarily taken, so that a reluctance to take it before the end of menstruation is understandable. But only 92 ever washed the vulva during menstruation, 17 of these doing so on special occasions only, and a good many only during the last day or two of the period. The reasons given for this lack of cleanliness varied from fear of a chill to fear of "crippling" and mental disease. Yet, almost all these girls were dainty in other matters of their toilet and underwear, and many expressed relief when told it was quite safe to have a bath while menstruating. The majority of the group used manufactured sanitary towels which they burned after use. Those with profuse loss were inclined to prefer home-made washable diapers. It is unfortunate that efficient sanitary towels are still relatively expensive to buy.

Dysmenorrhoea

As already pointed out, this series of patients is loaded with cases of dysmenorrhoea, and gives no information as to the true incidence of menstrual pain and lassitude among women in general. It is permissible, however, to analyse the nature of the pain experienced by these patients, and to search for any relation between its severity and some local and general conditions and symptoms. In order to do this the 200 patients were grouped into 5 classes or grades according to the severity of their dysmenorrhoea. (The correct definition of the term "dysmenorrhoea" will be discussed later. For the sake of convenience it is here taken to refer to local pain or discomfort.)

Grade 1 (30) Local menstrual pain or discomfort absent.
Grade 2 (61) Slight local discomfort sometimes or always.

Grade 3 (48) Usually a considerable amount of local pain.
Grade 4 (45) Pain really severe.
Grade 5 (16) Pain extremely severe.

(The numbers in brackets tell the total number of patients in each grade. When considering the *data* collected these totals should be kept in mind.)

The estimation of the degree of pain depended on the account given by the patient, but I tried to verify her statements by cross-questioning her about her symptoms and the extent to which they interfered with her recreation and with her ability to carry on with her work. It was interesting to find that one girl with slight local discomfort only (grade 2) had to give up because of vomiting, and another because of "dizziness," while a number cancelled certain engagements such as dancing because of the profuseness of the menstrual loss, and the general feeling of discomfort this caused, and not because of actual pain.

Type of pain. To find out whether particular types of pain were associated with different degrees of dysmenorrhoea the pain was classified as aching (including dragging), colicky and stabbing. It was enough (as it was when dealing with the site, time and duration of the pain), if a patient said she sometimes suffered from a particular type of pain, to be included in that class. In fact, many patients said they had aching and colic during one attack, and aching alone (rarely colic alone) during another. Aching pain was felt by 159 of the 170 patients who had any degree of dysmenorrhoea. Ninety-four of these complained of aching alone (grade 2, 55; grade 3, 27; grade 4, 11; grade 5, 1); 40 of aching and colic (grade 2, 4; grade 3, 8; grade 4, 20; grade 5, 8); 13 of aching and stabbing (grade 2, 1; grade 3, 6; grade 4, 6); and 12 of aching, colic and stabbing (grade 3, 2; grade 4, 6; grade 5, 4). Nine complained of colic alone (grade 2, 1; grade 3, 3; grade 4, 2; grade 5, 3); one of stabbing alone (grade 3), and one of colic and stabbing (grade 3). Some patients also complained of a dragging "falling-out" feeling which they referred to the vulva and vagina, and which was associated with hyperaesthesia of the vulva. A few volunteered that while the colicky intermittent pain was more acute, the aching pain was harder to bear because it lasted longer.

Site of the pain. All but 8 of the 170 patients who had some degree of dysmenorrhoea complained of pain in the lower abdomen. Eighty-eight said they had abdominal pain alone (grade 2, 35; grade 3, 28; grade 4, 20; grade 5, 5); 38 com-

plained also of backache (grade 2, 11; grade 3, 11; grade 4, 11; grade 5, 5); 15 of aching in the thighs as well as abdominal pain (grade 2, 6; grade 3, 3; grade 4, 4; grade 5, 2); and 21 of pain in the abdomen, back and thighs (grade 2, 2; grade 3, 6; grade 4, 9; grade 5, 4). Of the remainder 2 in grade 2 complained of backache alone and one of aching thighs alone, while 5 (grade 2, 4; grade 4, 1) complained of aching in the back and thighs.

Time and duration of the pain. Fourteen patients complained of premenstrual pain (grade 2, 11; grade 3, 1; grade 4, 1; grade 5, 1); 67 of pain during menstruation (grade 2, 31; grade 3, 17; grade 4, 13; grade 5, 6); while 84 said they had both premenstrual and menstrual pain (grade 2, 17; grade 3, 30; grade 4, 28; grade 5, 9). One (grade 2) had pain only after her period was over, one (grade 2) had pain before and after her period, while 2, both in grade 4, said they had pain before, during and after the period.

When the pain was premenstrual alone it generally lasted only a few hours, but sometimes up to 2 days. In the lesser grades of dysmenorrhoea menstrual pain generally lasted a few hours only, sometimes up to 2 days. In the more severe grades it commonly lasted 1 to 2 days. When the pain was both premenstrual and menstrual it often lasted for several days, especially in the severe grades. Colicky pain was almost always restricted to a few hours before or after the onset of the flow, when the aching pain was also at its worst. A few patients complained that they had occasional colicky spasms one or several days before or more than 12 hours after the onset of menstruation.

Variability of the pain. It was found to be the rule rather than the exception for girls in all grades of dysmenorrhoea to admit that the pain varied in intensity from month to month. Thirty-three patients (including 13 in grade 4, 4 in grade 5) stated that there was marked variability. Many in grade 2 and a few in grade 3 said that they often had no discomfort at all. One in grade 4 said that she occasionally had none. The grouping of the girls into the different grades of dysmenorrhoea was made in relation to their recent experience of pain. Careful questioning showed how often dysmenorrhoea had varied in severity at different periods in the life of the same girl, quite apart from any response to treatment. Only a small proportion of those now in grades 3 and 4 had had much the same amount of pain since they first began to suffer from dysmenorrhoea. The proportion in grade 5 was greater, but was still under 50 per cent

of the total number in that grade (7 out of 16). A considerable number in grades 2, 3, and 4 had at some time in their lives had more severe dysmenorrhoea. A number of patients had improved and relapsed more than once. The majority of those in grade 1 said they had never had any dysmenorrhoea, but 4 admitted they had had slight pain at some period of their lives, and one said the pain had been severe for a time. This variation in the severity of dysmenorrhoea from month to month, and at different times in the life of the same patient, besides adding to the difficulty of assessing the effect of any treatment, is a characteristic which must be given due weight in any discussion about the aetiology of dysmenorrhoea.

Condition after cessation of the pain. All but 33 of the patients who complained of dysmenorrhoea said they felt quite well after the pain had gone. This applied to those with severe as well as to those with slight pain (14 in grade 5, 38 in grade 4). Comparison of the general health and vitality, haemoglobin level and temperament between the whole group and those who continued to feel tired, showed that the tiredness had a closer relation to the state of health, and to the temperament of the patient, than to the severity of the dysmenorrhoea.

Condition of the uterus. A vaginal examination was possible, and was permitted in 127 patients. In 69 (because of their youth, because the hymen was unstretched, or because they preferred not to have a vaginal examination), a rectal examination was made. In 4 a pelvic examination was not made. In 130 patients the uterus appeared to be normal in size and position. Sixty-six patients showed some deviation from the normal: small uterus 7 (grade 1, 2; grade 2, 3; grade 3, 1; grade 4, 1); small with acute ante-flexion 18 (grade 1, 1; grade 2, 8; grade 3, 6; grade 4, 3); normal size with acute ante-flexion 13 (grade 1, 2; grade 2, 3; grade 3, 1; grade 4, 2; grade 5, 5); retroverted mobile uterus 18 (grade 1, 2; grade 2, 6; grade 3, 4; grade 4, 2; grade 5, 4); retroverted fixed uterus 3 (grade 2, 1; grade 3, 1; grade 5, 1; conical cervix 4 (grade 1, 2; grade 2, 1; grade 4, 1); one very large cervix (grade 1); one bulky uterus (grade 4); one fibro-adenoma (grade 4). In no patient was there any evidence of pelvic inflammation.

Onset of the menstrual flow. Eighty patients said that the menstrual loss was scanty for a few hours after it began; 104 said it began freely; 7 said the onset was sometimes scanty and sometimes free. In 9 the point was not investigated. The two

groups were very evenly distributed between the different grades of dysmenorrhoea.

Passage of clots and pieces of endometrium. Clots were noticed by 113 patients, by 43 on the 1st day of the period, and by the others on the 2nd or 3rd day. Eight patients said that the clots were as big as a walnut. The rest were of small size, and it seems likely that many were not true clots of blood, but consisted of blood and mucus mixed with disintegrating pieces of endometrium. Of the 8 girls who passed large clots, 3 were in grade 4 of dysmenorrhoea, and they thought that the passage of the clots was related to their pain; 4 were in grade 3, and one in grade 2, and in those 7 there did not seem to be any relation between the passage of clots and the pain. One girl said that she regularly passed "pieces of skin" ½ to 1 inch in size. She had never had any dysmenorrhoea.

Another patient has had severe dysmenorrhoea, most severe in her late teens, since shortly after the *ménarche*, and first noticed that she passed large pieces of endometrium when she was in her early twenties. I have seen pieces passed by her which seemed to form a complete cast of the uterine cavity. The loss had always been profuse—5 days every 28 to 34. In 1936 the loss increased—7 to 8 days every 28 to 34, and there was an occasional intermenstrual stain. In July 1937, when this patient was 36 years of age, a single fibromyoma, the size of a tangerine orange, was shelled out from the fundus of her uterus, and a right hydro-salpinx removed. Since then the menstrual loss has been much less—3 to 4 days every 26 to 31. The dysmenorrhoea, which had been gradually improving before her operation, and which varied in intensity from month to month, quite apart from the size of the pieces of endometrium passed, continued to improve. She is now (June 1941) free of dysmenorrhoea, though she still feels tired on the 1st day of the period. Large pieces of endometrium are still regularly seen.

Headache. Seventy-six patients complained of menstrual headache (grade 1, 9; grade 2, 18; grade 3, 23, and grades 4 and 5, 26). Thus, though the proportion was greater among those suffering from severe dysmenorrhoea, about 30 per cent of those who had slight or no pain complained of menstrual headache.

General fatigue. A feeling of general fatigue about the time of menstruation was complained of by 118 out of 170 patients of whom the question was asked. The proportion in each grade of dysmenorrhoea increased progressively with the severity of

the pain (grade 1, 36 per cent; grade 2, 65 per cent; grade 3, 74 per cent; grades 4 and 5, 86 per cent).

Alteration in mentality. Ninety-nine patients complained of some degree of irritability and depression, 24 of irritability alone, and 14 of depression alone. Of these 137, 54 said the change took place during the premenstrual period, 39 that it happened during menstruation, and 44 that it lasted during both the premenstrual and menstrual periods. In most patients the symptoms passed off within a day or two of the onset of the flow. Two girls felt irritable and depressed, and 2 others irritable only, after the cessation of the periods. Two girls said they felt the reverse of depressed—that they were more cheerful and "at the top of their form"—about the time of menstruation. Analysis of the 137 patients who complained of irritability or depression or both showed 13 to be in grade 1 of dysmenorrhoea, 37 in grade 2, 35 in grade 3, and 52 in grades 4 and 5. These symptoms are, therefore, seen to have been commonly experienced even by patients who did not complain of dysmenorrhoea, but the proportion rises steadily with the severity of the dysmenorrhoea to 85 per cent of those in grades 4 and 5.

Alteration in the action of the bowels. The bowels were said to move more freely than usual about the time of menstruation by 81 patients, and less freely by 39; change was not noticed by 72. Three said menstruation sometimes affected the bowels in one way, sometimes in the other, while 5 said they were inclined to be constipated in the premenstrual period but the reverse during menstruation. Classification of these 128 patients with menstrual alteration of bowel action, according to the severity of their dysmenorrhoea, gave: grade 1, 12; grade 2, 42; grade 3, 28, and grades 4 and 5, 46. In all grades alteration in the direction of looseness was much more common than the reverse, but the difference was less marked in grades 4 and 5.

Habitual constipation was complained of by 72 patients, the percentage increasing progressively from 23 per cent of those in grade 1 of dysmenorrhoea to 49 per cent of those in grades 4 and 5. Thirty-seven of these habitually constipated patients said that they were less constipated about the time of menstruation, though 16 were more constipated. Fourteen did not notice any change and 5 varied in their reaction.

These findings suggest that habitual constipation is a predisposing factor in the aetiology of dysmenorrhoea. On the other hand, the high number of patients, including over 50 per cent of those habitually constipated, who noticed a freer action

of the bowels than usual about the time of menstruation, makes one doubt the wisdom of the commonly given advice to all women who suffer from dysmenorrhoea to take an aperient at the beginning of menstruation.

Disturbance of micturition. Forty-four out of 169 patients of whom the question was asked, said they had noticed some frequency of micturition at the beginning of their periods. None had any retention or difficulty of micturition associated with menstruation.

Digestive disturbance. A considerable number of girls said they sometimes suffered from flatulence, nausea or loss of appetite about the beginning of their periods. Nineteen complained of vomiting, 10 in grade 5, 6 in grade 4, one in grade 3, and 2 (both "sometimes") in grade 2 of dysmenorrhoea.

Swelling and tenderness of the breasts. Ninety-nine patients reported premenstrual swelling and tenderness of the breasts, grade 1, 8; grade 2, 33; grade 3, 26; grades 4 and 5, 32. In most the symptom was present for a few days to one week before menstruation began and subsided very soon after the onset of the flow. A few noticed it for one day only, but several said that their breasts were tender for 10 days before the period began.

Skin changes. Ninety-one of the 161 who were questioned as to whether they had noticed a tendency to acne or other skin conditions about the time of the monthly period replied in the affirmative (grade 1, 10 out of 24; grade 2, 28 out of 50; grade 3, 23 out of 37; grades 4 and 5, 30 out of 50). Eighty-nine of these 91 complained of pimples on the face and neck, most often during the premenstrual week. Two complained of labial herpes in addition, one of labial herpes alone. One said she had pimples on her face and a general blotchiness on her face and neck as well, and one complained of general pruritus during the 1st day or two of the period. The premenstrual acne was almost always an exacerbation of a pre-existing condition. A number of girls with acne had not noticed any tendency to a premenstrual relapse. One girl said she had no skin changes but that stomatitis recurred each month.

General health and vitality. Taking all factors, including my knowledge of their clinical history, into account, I assessed 47 girls as having very good health and vitality (Class A), 105 as moderately good (Class B) and 48 as poor (Class C). Comparison of Class A with Class C with regard to dysmenorrhoea gave: *Class A*, grade 1, 7; grade 2, 21; grade 3, 8; grade

4 and 5, 11; *Class C*, grade 1, 7; grade 2, 11; grade 3, 17; grades 4 and 5, 13. If the grades 1 and 2 are taken together as representing slight or no dysmenorrhoea, and the result compared with the sum of grades 3, 4, 5, as representing an appreciable degree of dysmenorrhoea, we get, in the first instance, Class A 28, Class C 18, and in the second, Class A 19, Class C 30. The numbers in each class are small, and the difference between them might be accounted for by chance factors. At most these numbers might be taken to suggest that a condition of poor health and vitality provides favourable soil for the development of dysmenorrhoea. They do not afford any evidence that the state of health is a primary factor in its causation.

Nutrition. The nutrition of the patients was assessed clinically and by the use of Emerson's[1] tables of height-weight ratios, and the two results agreed very well. Seventy-two girls showed very good nutrition (Class A), 47 were slightly subnormal (Class B), and 81 definitely poor (Class C). Grouping the grades of dysmenorrhoea together as above, and comparing Class A with Class C, we get little or no dysmenorrhoea Class A 36, Class C 37, moderate or severe dysmenorrhoea Class A 36, Class C 44, a difference of no significance.

Haemoglobin level. The haemoglobin was estimated in all patients at least one week after the cessation of menstruation by the Neoplan (Hellige) haemoglobinometer in which 100 per cent is the equivalent of 14 grammes of haemoglobin per 100 c.c. blood. Sixty-six patients had over 96 per cent (Class A), 66 had between 87 per cent and 96 per cent (Class B), and 68 had less than 87 per cent haemoglobin (Class C). Of the last group 23 had under 80 per cent. Analysis as above showed, little or no dysmenorrhoea Class A 31, Class C 32, moderate or severe dysmenorrhoea Class A 35, Class C 36. Analysis of 23 patients with haemoglobin under 80 per cent showed grade 1, 3; grade 2, 8; grade 3, 3; grades 4 and 5, 9. These figures do not suggest any aetiological relation between anaemia and dysmenorrhoea.

Temperament. Temperament is a very difficult matter to judge. With some diffidence I classed 75 patients as "level-headed," 73 as "highly-strung" and 52 as "neurotic." Among the "level-headed" 44 had slight or no dysmenorrhoea, while 31 had moderate or severe dysmenorrhoea. In the "highly-strung" group the corresponding figures were 23 to 48, and in the "neurotic" 22 to 30. These figures suggest that dysmenorrhoea may develop more readily in women who have a "high-

ly-strung" or "neurotic" temperament though the considerable number of "level-headed" patients who suffered from severe dysmenorrhoea must be kept in mind.

The age of the patients, the amount of exercise they took, their occupation, the time spent in work and travelling and their home conditions were also studied in relation to dysmenorrhoea. The smallness of some of the groups, however, and the wide disparity in numbers made comparison difficult, and results of any significance were not obtained.

Discussion

(1) *Menstrual irregularities.* The findings of the present study with regard to variations in the age of onset, regularity and duration of menstruation, and the amount of the menstrual loss of blood agree with those of other investigators in showing that there is no one standard which can be applied to all women at all times. The duration, amount and regularity of menstruation all vary to some extent, not only between different women, but from time to time in the experience of the same woman. Even considerable variations from the average need not of themselves have any serious significance. They must be considered in relation to the previous history of the individual and the state of her general health and well-being. Therefore, when treating patients with delayed onset, irregular, scanty or profuse menstruation, it is advisable to direct attention first towards improving the general health, and to inquire into and try to eradicate unfavourable circumstances in the patient's environment. A further important part of treatment is to reassure her (and her mother) that she is in all probability functionally sound. Difficult as it may be for us to believe it, many women still fear that serious illness, e.g. mental disease, may follow the missing or alteration in amount of a few monthly periods, and girls in whom the *ménarche* is later than usual are often made unduly anxious about it by the attitude of their mothers. Out of this anxiety neuroses are very prone to develop, and these neuroses can, by themselves, lead to further aberrations of function. This is not to deny the therapeutic value of the ovarian and pituitary hormones, whose *rôle* in controlling menstruation is now well understood. As yet, however, most of the results obtained by their administration are of a substitutional type only. They cannot yet be used with confidence in doses which will stimulate individual hypoplastic organs to normal development

and function. In many cases the endocrine disturbance seems merely to be the mechanism by which abnormal stimuli, originating elsewhere, exert an influence on the pelvic organs, and not the primary cause of the trouble. The indiscriminate use of these hormones in the present state of our knowledge can only lead to disappointment. They should be reserved for carefully selected patients who have failed to respond to general measures.

(2) *Dysmenorrhoea.* Dysmenorrhoea may be classed as primary in the absence of pelvic disease, and secondary when menstruation merely exaggerates the symptoms of pelvic disease which are already present. This study deals only with primary dysmenorrhoea. Many gynaecologists distinguish between two types of primary dysmenorrhoea, severe colicky intermittent pain and constant aching pain. The latter is generally considered to be caused by pelvic congestion. Moir[2] considers that the former has its origin in a spasm of the uterine muscle, or in the local ischaemia produced by the force of the uterine spasm. With this differentiation goes a tendency to regard at least the lesser degrees of the aching type as unimportant, even physiological. Eden and Lockyer[3] state, "In only a small proportion of the women of civilized races is the menstrual function absolutely painless. A certain amount of discomfort, general or local, commonly accompanies menstruation even in women in normal health."

The number of cases in the present series is small, and one must be careful not to attach undue importance to findings which may have been influenced by chance factors. However, any acceptable theory of the aetiology of dysmenorrhoea must be in agreement with clinical experience. It is, therefore, legitimate to inquire how some of the more important of the many theories which have been propounded accord with the evidence provided by the patients studied in this investigation.

Immediate cause of the pain. The commonest type of pain complained of by my patients was an ache. Intermittent colicky pain was the rule in the severe cases of dysmenorrhoea but was also present in some of the slight cases. Most patients who had severe dysmenorrhoea complained of both aching and colicky pain, though a few complained only of intense colic and a few only of aching. Colicky pain was almost always restricted to 1 or 2 hours before or after onset of the flow, when the aching pain was also at its worst. The aching pain was much more variable in time and duration. It was also much more variable in site. Though commonly felt in the lower abdomen it was often

felt in the back and thighs. Colicky pain was always referred to the lower abdomen.

Both types of pain vary in severity. The aching may be no more than a slight heavy feeling, or it may be severe and neuralgic. In character it resembles the oppressive pain of some other lower abdominal conditions. A woman trying to describe the pain associated with colitis will say, "It was just like my courses coming on." Patients with pelvic inflammation will often say, "It is like having a monthly pain all the time." The chief characteristic of the colicky pain is its intermittency, though the spasms may follow one another very quickly, and the aching pain is generally present between them. Severe attacks are acknowledged by patients who have had both conditions to be very similar to the pain felt before the expulsion of the ovum in abortion, or that felt towards the end of the 1st stage of labour.

The distribution of all visceral pain is segmental in character, depending on the nerve supply of the particular organ or organs affected. The site of the pain in dysmenorrhoea is consistent with an origin in the uterus but does not exclude an origin in neighbouring structures. Moir's experiments related to cases of severe uterine colic only. Whether the aching pain represents a lesser response of the same reaction which produces spasm of the uterine muscle, or whether it is a different type of reaction, and whether pelvic congestion plays any part in its production can only be settled by further experimental research.

However, the variation in the severity of the pain from month to month and at different age periods, shown by so many of my patients, and the fact that both aching and colic might be felt during one attack and aching alone (rarely colic alone) during another, have persuaded me that there is no justification for making a distinction clinically between patients who have uterine colic and those who have not, and that we must study patients who have slight pain as well as those who have severe pain if we are to understand the true nature of the underlying cause of primary dysmenorrhoea.

Mechanical obstruction, malposition and hypoplasia of the uterus. The uterus is a mobile organ. Its position varies to some extent with the condition of the neighbouring bladder and bowel. Its size also varies somewhat between different women and in the same woman at different periods of the menstrual cycle. It is, therefore, difficult by clinical examination to decide whether a uterus which shows some deviation from the average

size and position may yet be functionally normal. For example, the very small uterus often found in a nursing mother is perfectly healthy, and a woman with a small acutely ante-flexed uterus may become pregnant very soon after marriage. Underdevelopment and malposition of the uterus, however, are considered by many gynaecologists to be a factor in the production of dysmenorrhoea, and it is reasonable to suppose that whatever the nature of the underlying cause, its effect may be modified by local pelvic conditions.

In the present investigation a relation was not found between dysmenorrhoea and a scanty or profuse onset of menstruation. Of the 196 patients in whom a pelvic examination was made 33 per cent of those in grade 5 and 75 per cent of those in grade 4 of dysmenorrhoea were found to have a well-developed and normally placed uterus, while 33 per cent of those in grade 1 and 36 per cent of those in grade 2 were found to have a uterus which deviated in some way from the normal. It seems, therefore, that hypoplasia and malposition of the uterus, while they may determine the production of colicky pain in a predisposed individual, do not *per se* cause dysmenorrhoea. The passage of clots sounds a very likely cause of pain, but the majority of my patients who had dysmenorrhoea, did not pass any clots of appreciable size, and even the small clots noted were most often passed on the 2nd or 3rd day of menstruation, after the pain was over. Though some patients associated the pain with the passage of clots, several who passed large clots had very little dysmenorrhoea.

The variation in the severity of the pain at different periods of their lives reported by many of the patients, and the well-known fact that dysmenorrhoea is comparatively rare during the first few years after the *ménarche*, also argue against the theory that a developmental defect is an important factor in the aetiology of dysmenorrhoea. Moreover, dysmenorrhoea was relieved in many patients in the present series who had an acutely ante-flexed or retroverted uterus, although an attempt was not made to interfere with these conditions.

Excessive menstrual decidua. Beckwith Whitehouse[3] suggests that excessive or abnormal production of decidual cells in the endometrium, due to dysfunction of the anterior pituitary and ovarian hormones, is an important cause of dysmenorrhoea. He thinks that pain is probably associated not with the expulsion of pieces of endometrium from the uterus but with their separation from the uterine wall. He considers that retention of some

of these pieces in the uterine cavity may, by irritation, cause excessive decidual formation during the next cycle, and conversely, complete evacuation may be followed by a lesser reaction. This would explain the intermittency of the pain.

As pointed out above, several patients who passed clots had little or no dysmenorrhoea. The case of membranous dysmenorrhoea, however, already described, provides the best evidence against this theory. Though the patient continues to pass large pieces of endometrium she has not any discomfort.

Sympathetic neuritis. Davis[4, 5] found evidence of subacute or chronic neuritis in 70 per cent of a number of sympathetic nerves removed by presacral sympathectomy from women with severe dysmenorrhoea. He suggests, "Whatever the nature of the abnormal impulses which cause dysmenorrhoea, they are initiated or at least exaggerated in their passage through sympathetic nerves rendered abnormally sensitive by previous inflammation."

There is some difference of opinion as to whether the microscopic appearance of the presacral nerves as described by Davis is definite evidence of an inflammatory process. It is theoretically possible that repeated attacks of severe uterine spasm might lead to changes in the nerves supplying the uterus which might in turn exaggerate the spasm. It is also understandable that interruption of the tracks by which the impulses which cause dysmenorrhoea—whatever these are—may be transmitted, as by presacral sympathectomy, would relieve the pain, though some explanation must be found to account for the failures following this operation. The variability of the pain from month to month shown by many patients suffering from dysmenorrhoea, the occasional severe attacks of pain in women who generally have little or no dysmenorrhoea, and the well-being of the majority as soon as their pain has ceased, are clinical facts, however, which make it unlikely that presacral neuritis is an important factor in the aetiology of primary dysmenorrhoea.

Hormonal imbalance. The changes in the genital organs which are associated with the menstrual cycle are now known to be brought about through the agency of the anterior pituitary and ovarian (follicular and corpus luteum) hormones. It may well be that the balance of some or all of these hormones will be found to be disturbed in cases of dysmenorrhoea, when methods for their estimation in the blood and urine are more precise than at present. Some of the symptoms which accompany dysmenorrhoea, e.g. the flushed sweaty feeling and the emotional in-

stability, are very similar to menopausal symptoms and suggest a hormonal imbalance. But it does not follow that an endocrine disturbance is the primary cause of dysmenorrhoea, or that the correct treatment is to try to adjust it by the administration of oestrin, progestin or anterior pituitary hormone. The variability of the pain from month to month, to which attention has already been drawn several times, and the fact that severe dysmenorrhoea has been cured by many different kinds of treatment, argue against any associated hormonal imbalance, if it does exist, being due to any dysfunction of the endocrine glands.

Now, if the primary impulses which cause dysmenorrhoea are not initiated by morbid processes in the endocrine glands or pelvic nerves, but are merely transmitted to the pelvis through hormones or nervous tracks, it follows that any changes in hormonal balance or in the histology of the pelvic nerves, which are found to be associated with dysmenorrhoea, become of less importance than the conditions, constitutional or psychological or both, in which these impulses originate. "We speak glibly of disturbances in the endocrine system which lead to the hypofunction or hyperfunction of the various physiological processes in the human being. However, we do not seem to go sufficiently far back in our diagnosis to discover the causes that lead up to such disturbances in the endocrine cycle." (Miller,[6] quoted Dunbar.)

Constitutional and environmental conditions. There must be very few women who have not experienced a moderately severe attack of dysmenorrhoea. It seems likely that dysmenorrhoea can be an associated symptom of many conditions, e.g. a chill, an emotional shock, which temporarily depress physical or mental well-being. The analogy with headache is close. But such constitutional conditions, accidentally associated with menstruation, cannot explain recurring dysmenorrhoea whether mild or severe. It has been suggested that dysmenorrhoea is a manifestation of spasmophilia (Hirsch[7]). McDowell[8] and Schwarz and Smith[9] consider it to be an allergic state. Though either of these conditions may play a part in the development of individual cases, it is impossible to believe that they provide an explanation for all cases. Experience with individual patients leaves me in no doubt that all kinds of unhappy physical and emotional circumstances, while they may be without effect on some women, predispose to the development of dymenorrhoea in others.

Analysis of the records of patients in this series affords no

evidence of a direct aetiological relation between dysmenorrhoea and any of the particular constitutional and environmental conditions considered, though it suggests that habitual constipation is a predisposing factor, and that a low level of general health and vitality, and a highly-strung or neurotic temperament provide more favourable soil for its development than do a high level of general health and vitality or a level-headed temperament. These conditions also favour the development of psychogenic factors. Emotional upsets and minor disturbances of function are less likely to make a permanent impression on those who are emotionally stable and enjoy a high standard of health than on their less fortunate sisters.

Psychogenic factors. Many women will admit that they have less severe dysmenorrhoea when they are having a happy time on holiday. Johnstone[10] relates that many of his patients who suffered from dysmenorrhoea before the last war were entirely free from pain when they were driving ambulances in France or doing other strenuous and exciting war work, but relapsed when they returned to an aimless existence. This suggests that there is a psychogenic factor in the aetiology. So does the common experience of variation in the intensity of the pain from month to month, and the feeling of well-being once the pain is over. It is well known that dysmenorrhoea is often cured by marriage, and particularly by child-birth. It is less often remembered that dysmenorrhoea may be worse after marriage. It is sometimes, though rarely, worse after child-birth, but when this happens it is explained (no doubt often correctly) as being due to pelvic inflammation.

Recent researches into the integration of the endocrine system, and the relation between the cerebral cortex, the diencephalon and the pituitary gland, are beginning to throw light on the mechanism by which such psychic influences can affect ovarian and uterine function. Langdon-Brown[11] points out that whereas the endocrines were first regarded as an autonomous system acting independently of the central nervous system, the newer conception postulates a controlling centre in the diencephalon. The diencephalon has ties in three directions: with the cerebral cortex above, with the pituitary gland below, and with the sympathetic nervous system, "of which it appears to be the head ganglion. . . . In this way a psychical experience may record its effects either through the chemical mechanisms initiated through the pituitary, or on the sympathetic acting on the viscera or on other ductless glands." Riddoch[12] states, "The

diencephalon is, without doubt, not only the head ganglion of the vegetative nervous system, but is also the central nervous mechanism for emotional response in health, under the control of the cerebral cortex.'' Kunz[13] considers that probably every visceral function is subjected to influences exerted by the psyche and emotional states through the autonomic and endocrine systems.

The presence of a psychogenic element in dysmenorrhoea has, indeed, long been acknowledged, but gynaecologists have been slow to admit that psychological factors are of primary importance in the aetiology, while psychologists have little opportunity to study any except the most severe types of dysmenorrhoea.

Novak and Harnik[14] accept the aching pain as being due to the expulsion of clot or membrane, or to an unusual degree of pelvic hyperaemia, but think that every case of true uterine colic has its origin in a psychic trauma. This has most often a sexual basis, but may originate in some other emotional crisis which has only an accidental relation to menstruation. The first attack of dysmenorrhoea having been thus produced, succeeding attacks are due to fear of the repetition of the pain, and an inferiority complex engendered by the conviction that something is wrong with the sex organs (''Genitalkrank''). Cure results when the original psychic trauma is brought to light, and its *rôle* in the production of her dysmenorrhoea explained to the patient. This can usually be accomplished in one or two interviews, but cases of exceptional difficulty need psycho-analysis. These authors base their conclusions on their clinical experience of 247 cases of severe uterine colic collected over a period of 4 years.

While acknowledging a debt of gratitude to Novak and Harnik, whose thesis clarified for me much that had previously been obscure in the behaviour of my own patients, I do not think it is legitimate, for reasons already stated, to make a rigid distinction, as they do, between the origin of cases of uterine colic and the origin of cases of aching dysmenorrhoea. To say that the lesser degrees of dysmenorrhoea are the result of excessive pelvic hyperaemia is not enough. We want to know what factors bring about this condition in so many women, just as we want to know what factors cause uterine colic. Secondly, Novak and Harnik's definition of the psychic traumata capable of causing dysmenorrhoea is so wide that it must be possible to find one or more in the lives of most women. It is another matter to relate such an occurrence to the onset of dysmenorrhoea in an individual

patient. Though there was in some of my patients a history of an emotional disturbance (e.g. alarm at the first monthly period, shock at hearing a brutal explanation of sex, unhappy love affair) associated with the first definite attack of dysmenorrhoea, I have not been able to convince myself that this was always or, indeed, often so, even in the severe cases. (This may, of course, simply mean that I did not discover it.) Though dysmenorrhoea frequently, in my series of patients, became more severe during a period of mental stress, the increase in pain was more often gradual than abrupt. Similarly, though sudden dramatic cures were produced in some, improvement was more often slowly progressive and subject to relapse.

As my investigation went on I became increasingly impressed by the ignorance of my patients about the true function of menstruation, and by the atmosphere of superstition and exaggerated reticence with which they surrounded it. Excluding two medical women, only one girl had an approximate idea of its real significance. Most thought it a "cleansing" process—"You get rid of your bad blood." The majority had been taught to fear the use of soap and water during their periods, for reasons which varied from fear of a chill to fear of "crippling" and mental disease. It is still, in my experience, the rule rather than the exception for a girl to be unprepared for the onset of menstruation, and when the bleeding begins she is not usually given any rational explanation, but only a vague story that it means she is "becoming a woman." This whets her curiosity without allaying her apprehensions, which are increased by petty restrictions on her activities during menstruation, especially when her natural rebellion against these is countered by an anxious mother's mysterious warnings about the serious consequences to health and happiness if the advice is disregarded.

When following the progress of my patients, I was surprised at the frequency with which those girls who had irregular, scanty or profuse menstruation reported about this before mentioning the condition of their dysmenorrhoea. One probably spoke for many when she said she was worried about her scanty periods in case it "made any difference to her after she was married." The lesser degrees of dysmenorrhoea were accepted as normal, but in cases of severe dysmenorrhoea I was impressed—as Novak and Harnik had been—not only by the patient's dread of return of the pain, but by her deeply rooted fear that she must be functionally unsound to have such pain. Not all patients openly confessed to this fear, but there was no doubt of their gratitude

and relief when assured that there was no foundation for it. Although they may be ignorant about the physiology of menstruation all women know it is connected with their biological function of child-bearing, and it is of deep concern to every normal woman that she should be capable of performing this function when the time comes. A feeling of resentment at the woman's *rôle* is far less common than one of frustration because life is not providing the opportunity to carry it to fruition.

An anxious and ignorant attitude to menstruation is not confined to the working-class. Much the same ideas still prevail in the middle and upper classes in spite of the efforts of a few enlightened girls' schools. I suspect that the reason for this state of affairs is due less to the fact that menstruation is an unaesthetic bodily function and a manifestation of sex than to the influence of old beliefs and customs. When we remember the extraordinary properties which have been attributed to the menstrual lochia, and the many taboos and even persecutions to which menstruating women were in former times subjected (illuminatively described by E. Novak[15] and Ploss and Bartels[16]), we need not be surprised that some misconceptions about menstruation still persist.

Another factor which has helped to perpetuate a pathological attitude to menstruation has been the widely held belief that there is a physiological depression of the mental and physical faculties of all women about the time of menstruation. The chief difficulty in arranging experiments to prove or disprove this contention is the elimination of extraneous physical and mental stimuli, which can by themselves influence functional capacity. Failure to do this probably accounts for the conflicting results. Two interesting studies on this subject have been published by the Industrial Fatigue Research Board,[17] and their results have been broadly confirmed by Hubert.[18] Briefly, they found that any periodic variation in metabolic processes and functional efficiency due to the menstrual cycle, if it did exist, was of small magnitude and was overshadowed by fluctuations due to everyday accidental experiences, which are a commonplace in the lives of all men and women.

Most people—some more than others—suffer from occasional attacks of headache, fatigue, depression and other minor complaints. Most of us are occasionally glad of an excuse which will allow us to slacken off from our duties for a few hours without loss of self-respect; and most of us forget the wish for such self-indulgence when we are engaged in some pleasurable or

exciting occupation. Women have not only been encouraged to regard menstruation as a sufficient excuse for any slackness on their part, they have been conditioned to expect depression of function and minor ailments during their periods (cf. descriptions in common use, "poorly-time," "ill-period"), and warned that direful consequences will follow neglect of the advice to regard themselves as semi-invalids for a few days out of every month.

I suggest that in this prevailing attitude to menstruation is to be found the primary factor which predisposes so many women to the development of dysmenorrhoea. Interruption of normal activities tends to exaggerate accidental fluctuations in mental and physical capacity and conduces to local discomfort, especially in the presence of chronic constipation. It also, particularly in adolescence, helps to focus attention on menstruation and on the sex function with which menstruation is known to be associated. Thus the way is prepared for the development of severe dysmenorrhoea during periods of emotional stress. My view of the importance of women's attitude to the function of menstruation is not at variance with Novak and Harnik's theory of psychic trauma, it is complementary to it. In effect, I am suggesting that in all degrees of primary habitual dysmenorrhoea, not only in cases of severe uterine colic, the essential aetiological factor is psychological. Constitutional, environmental and perhaps local conditions merely act as subsidiary factors in susceptible individuals. It follows as a natural corollary that I think Sanderson Clow[19] is right when she says, "When menstruation is normal, the girl is free from any pain, headache, sickness or feeling of discomfort." I do not think we can deal effectively with the problem of dysmenorrhoea until this definition is accepted and attention paid to the slight as well as to the severe cases.

Treatment

1. *Preventive.* If this view of the cause of dysmenorrhoea is right, it becomes of primary importance that girls should be taught to regard menstruation as a normal function which should interfere with none of their usual activities. Most medical authorities now agree that this is advisable, but some still hesitate to allow strenuous games and sports to be continued during the periods (Davis[5]). It is important that this attitude should be changed. To forbid during menstruation any activity undertaken at other times, on the ground of its effect on health, inevit-

ably fosters a menstrual inferiority feeling in a girl, which predisposes her to the development of dysmenorrhoea. The experience of some progressive girls' schools should be sufficient to prove that strenuous exercise during menstruation does no harm whatever to a healthy girl.

The question of adolescent instruction in sex is a thorny one. My own belief is that it is much better for a girl to learn the physiological facts of reproduction before her own emotional reactions to sex become acute. The basis of such instruction can be easily and naturally found in lessons on natural history. It would undoubtedly help to kill some of the harmful superstitions about menstruation, and encourage a healthier attitude to it if all girls were given an outline of the physiology of the menstrual cycle before they left school. The emotional relation makes such a task difficult for a mother, even if she has the necessary knowledge. Some teachers are qualified and well fitted to undertake it, others are not. As a rule the school doctor is probably the most suitable person. She can use the opportunity to give advice about menstrual hygiene, and explain that minor variations in the regularity and amount of the menstrual loss are without serious significance, and so forestall anxiety on this account. I have seen nothing but good come from such instruction. With the aid of diagrams it can be given very simply.

2. *Curative.* The measures outlined above are equally applicable in the treatment of mild dysmenorrhoea. It is, of course, more difficult to bring about a robust attitude to menstruation in girls who have already learned to be anxious about it. It is often necessary to give continued encouragement. (A useful leaflet to supplement the spoken word, entitled "Advice to Young Women concerning the Monthly Period," has been drawn up by members of the Medical Women's Federation and is published by H. K. Lewis and Co., London.) Individual patients present particular defects which call for correction, e.g. habitual constipation. When girls are taught to regard menstruation as a normal function which should not interfere with any of their usual activities, and when mild degrees of dysmenorrhoea cease to be ignored by doctors, many fewer cases of severe incapacitating dysmenorrhoea will develop. When these do occur, however, two things are of fundamental importance in treatment: (1) to convince the patient that the pain does not arise from disease or imperfect development of her genital organs, and (2) to mitigate her dread of its monthly recurrence. The first is best brought about by a thorough physical examina-

tion and an explanation of the physiology of menstruation, the mechanism of the production of her pain, and the influence of her emotions, especially fear, in exaggerating and bringing about its recurrence. The physical examination gives her confidence that one's opinion that she is functionally sound is based on knowledge. It also brings to light any constitutional defects which may be contributing factors in increasing her susceptibility to dysmenorrhoea, and enables them to be dealt with. This alone may cure the dysmenorrhoea. The explanation of the physiology of menstruation and dysmenorrhoea, however, relieves fears and answers questions of which she is only half conscious and often cannot put into words, and makes her permanent recovery more likely. In other words, such an explanation often removes the harmful effect of psychic traumata and makes it unnecessary to probe into their precise nature in individual patients.

Once the dysmenorrhoea begins to be relieved progress will probably be rapid, for the patient has now more confidence in what she has been told, and loses some of her dread of a return of the pain. But occasional relapses may be expected, especially if she meets unhappy personal or environmental circumstances. It is, therefore, important that she should be kept under observation and encouraged from time to time. There is no objection to the use of simple sedative drugs in conjunction with this treatment. By relieving the pain they take away some of the dread of its recurrence. But their mode of action should be explained to the patient so that she does not come to rely on them unduly. In the most severe cases exercise is impossible during the acute pain. But patients should be encouraged to continue exercise if they possibly can. It certainly relieves the pain if it is persisted in, though I think that too much credit is given to the exercise, and too little to the change in the mental attitude which takes place when a girl finds by experience that she can carry on with her normal activities during menstruation without harm.

The response of my patients to these methods of treatment has encouraged me to believe that it is unnecessary in most cases, even of severe dysmenorrhoea, to use those adopted by Novak and Harnik which are essentially psycho-analytic in character. However, if the pre-eminent influence of psychogenic factors is admitted, psycho-analysis becomes the rational treatment for patients who are not cured by these simple methods, and some of my patients have been treated, with benefit, at a

psychological clinic. Surgery ought to have no place in the treatment of primary dysmenorrhoea. At best it cures by suggestion. If an operation fails to cure the patient, or if she relapses later, the fact that an operation was thought necessary convinces her that there was indeed something wrong with her pelvic organs, and this conviction makes her subsequent cure more difficult.

Results of treatment. Dysmenorrhoea has been cured by many different methods. A record of successful cases is, therefore, no proof that a theory of aetiology is right. Those of the present series who were found at their overhaul to have severe dysmenorrhoea, or some defect of health which needed attention, have naturally made more frequent subsequent attendances, and have afforded me more opportunity to give encouragement after any relapse. Three years after the examination of the first and 2 years after the examination of the last patient included in the group the results were as follows:

In grade 5 of dysmenorrhoea 6 patients had little or no discomfort, 4 had very much improved, 3 had improved, 2 were *in statu quo*. The remaining woman, who was worried in case she was sterile, became pregnant before the next monthly period following her examination. In grade 4, 18 patients had little or no discomfort, 14 had very much improved, 5 had improved, 5 were *in statu quo*, one had improved very much but relapsed when she developed appendicitis (pelvic), 2 had not reported. In grade 3, 25 patients had little or no discomfort, 6 had very much improved, 8 had improved, 2 were *in statu quo*, 5 had not reported, one was worse, one had died (chorea gravis). In grade 2, 19 had no discomfort, 6 had improved, 7 were *in statu quo*, 28 had not reported, one was worse.

Summary and Conclusions

Two hundred young women, 189 of whom came under National Health Insurance, and 170 of whom suffered from some degree of primary dysmenorrhoea, were given a thorough physical overhaul, including a pelvic examination, and detailed notes were made of their menstrual history, their environment and habits.

The age of onset of menstruation varied from 10 to 19 years, 83 per cent being between 12 and 15 years. Few had absolutely regular periods. Many healthy girls who were generally regular to within a few days had had periods of temporary irregularity.

The patients were divided into 5 groups according to the severity of their dysmenorrhoea. In each group an analysis was made of the nature and duration of the pain, the development and position of the uterus, the association of certain distant menstrual symptoms (e.g. headache, fatigue, skin changes) and the presence of some conditions of general health and temperament.

The more important theories of the aetiology of dysmenorrhoea are critically reviewed in the light of the clinical experience gained during the investigation. The conclusions arrived at may be summarized as follows: (1) Normal menstruation should be free from all pain and discomfort and should not cause depression of physical or mental capacity. At present the majority of women are predisposed to the development of dysmenorrhoea by their ignorance of the true nature of menstruation and the lingering influence of old superstitions and taboos. This predisposition is increased by any interruption of usual activities during the periods. (2) Isolated attacks of dysmenorrhoea may be due to many conditions (e.g. chill, emotional shock) accidentally associated with a menstrual period, and are of no importance in themselves. Habitual menstrual malaise, however, makes their repetition easier. Dread of a return of the pain and fear of functional incapacity appear with succeeding attacks and greatly increased the likelihood of severe dysmenorrhoea becoming established. (3) Particular constitutional and environmental conditions act as subsidiary factors in susceptible individuals. (4) All girls should be taught to regard menstruation as a normal function which should interfere with none of their usual activities. They should be given an outline of the physiology of the sex cycle and the facts of reproduction before their own emotional reactions to sex become acute. In the treatment of established dysmenorrhoea an explanation should in addition be given to the patient of the mechanism of the production of the pain, and the part played by her emotions, especially fear, in causing its recurrence. Her anxiety about the health and development of her sex organs must be relieved. Any constitutional or environmental defect should be dealt with. Patients who do not respond to these measures should be referred to a psychologist. (5) Surgery ought to have no place in the treatment of primary dysmenorrhoea.

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Observations on the Aetiology and Prophylaxis of Prothrombin Deficiency and Haemorrhagic Disease in the New-born*

BY

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So long ago as 1913, in a post-mortem investigation upon the blood of a fatal case of haemorrhagic disease Whipple[1] found complete absence of prothrombin. For many years this observation was neglected, but with greater understanding of the mechanism of blood coagulation and with the recent development of methods of prothrombin estimation by the use of venous and capillary blood (Quick,[2] Warner,[3] Kato[4] and others), it has been confirmed by several workers (Brinkhous[5] *et al.* and others) and has been extended in that some degree of hypoprothrombinaemia has been shown to be the rule in the new-born infant. When this becomes extreme, blood clotting is abnormally slow and persistent haemorrhage results. Cure of this prothrombin deficiency by administration of vitamin K or vitamin K-analogues to the child and its prevention by giving the preparation to the labouring mother have both been clearly demonstrated (Shettles[6] *et al.*, Macpherson[7] *et al.*), but the possible origin of the condition has been given scant attention. Some years before the importance of prothrombin in relation to certain of the haemorrhagic states was recognized, Kugelmass[8] reported the successful prophylaxis of haemorrhagic disease of the new-born by careful supervision of the diet during one pregnancy and the recurrence of the condition after the next pregnancy in which such supervision had been refused. More recently, Kato and Poncher,[9] though they made no direct study of the dietary habit of their patients, drew attention to the fact that most of them were from families of a low social stratum. Most investigators, however, have been influenced by the elucidation of the circumstances which promote prothrombin deficiency experimentally

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and in the adult, and have suggested such causal factors as low reserve of vitamin K in the foetus, inadequate supplies of the vitamin in the diet of the newly born infant, deficient fat absorption (Grossman[10]) and the sterility of the intestinal contents at and for a short time after birth.* (Quick and Grossman.[11]) The subnormal values of prothrombin found in cord-blood (Macpherson *et al.*, Javert and Moore[12]) and the occasional onset of bleeding in haemorrhagic disease at or within a few hours of birth imply a low reserve in the foetus and, therefore, demand further explanation that cannot be adequately given by theories postulating abnormalities of foetal intake or absorption alone. Further, the fact that a big increase in the vitamin K intake of the mother a few hours before delivery prevents the usual fall in the prothrombin index in the child suggests that the origin of the deficiency lies in the antenatal period. Support for this argument and the inspiration of the present investigation were found in the close similarity of readings in two pairs of uni-ovular twins (Table I) and in three statements made in a previous paper (Macpherson *et al.*) namely:

1. The prothrombin index of the blood of the umbilical cord varied distinctly with that of the mother at the end of labour.

2. The variation in the prothrombin index of the blood of the umbilical cord did not apparently bear any relation to any feature of labour or delivery.

3. The extent of the decrease in the prothrombin index neonatally varied with the prothrombin index of the blood of the umbilical cord.

This paper reports, from the results of an investigation extending over a period of more than 12 months, an attempt to assess the influence on the neonatal prothrombin index of the following factors: maternal diet during pregnancy, prematurity, toxaemia, prolonged labour, neonatal abnormalities.

Methods

Two methods, which were found to give closely similar results when compared in the same cases, were used for the estimation of prothrombin.

1. A modification of the method of Ziffren,[13] in which 1 c.c.

*Certain bacteria, e.g. staphylococci, *b.* coli, *b.* tuberculosis, *b.* subtilis, have the power to synthesize vitamin K, which is freed for absorption when the bacteria are killed in the intestine.

of venous blood is mixed with 0.1 c.c. of a thrombokinase solution in a small tube immersed in water at 37°C., and the time required for clot formation is taken.

2. The capillary blood method developed in this hospital has been used as described by Innes and Davidson[14] with the following modifications:

(*a*) The solutions are kept at a constant temperature.

(*b*) The oxalated blood was diluted with four times its own volume of normal saline.

(*c*) Latterly a lecithin-venom solution (Hobson and Witts[15]) was used as the clotting agent. Comparison on the same cases showed that almost identical readings were given by Russell viper venom and lecithin-venom solutions, but that when the prothrombin deficiency was very pronounced, a sharper end-point was obtained with a lecithin-venom mixture. All readings are expressed as a percentage of normal prothrombin clotting time, the "Prothrombin Index" (Illingworth[16]). It must be pointed out that these methods (and also Quick's) are not an accurate measure of the prothrombin content of the plasma, but give an indication of the clotting activity of a solution of blood in which, provided there is no serious deficiency of fibrinogen, the quantity of prothrombin and the ease with which it can be converted into thrombin are the only variables.

During the latter part of this investigation it has not been possible to make prothrombin estimations on the blood of the mother and umbilical cord at the time of delivery. When the mother was already an in-patient, her prothrombin index was estimated as nearly as possible at the beginning of labour. In patients admitted for delivery only, the estimation was done on the 1st day of the puerperium. Under these conditions the prothrombin index of the mother has been found to be consistently higher than at the end of the 2nd stage of labour.

Investigation

(1) *Diet*

The richest sources of vitamin K in nature are green leaves, and of those leaves which are most commonly eaten, spinach, cabbage, and cauliflower contain the greatest quantities of the vitamin. The heart of the vegetable contains appreciably less vitamin K than do the outside leaves. Milk and egg-yolk contain a smaller and variable amount of vitamin K; meat still

smaller amounts, and root vegetables and fruits practically none at all.

According to Mellanby[17] the ideal diet in pregnancy should contain a daily ration of 2 pints of milk, 2 servings of green vegetables, 1 to 2 eggs, fresh fruit and cod liver oil, with sea-fish 3 times and liver once a week. At present it is certain, and at any time it is probable, that such a diet is beyond the reach of the average hospital patient. Dietetic histories obtained by close questioning of the patients on this everyday and hence ill-remembered subject have, therefore, been divided with reference to the intake of foods rich in vitamin K into Adequate and Deficient. An adequate diet must contain, in addition to coarse cereals, carbohydrates and root vegetables, a daily allowance of not less than 1 pint of milk; of green vegetables, preferably a daily serving, and certainly not less than 5 servings a week; meat or fish daily and a full weekly allowance of butter and other fats. A diet was considered to be deficient either when one item rich in vitamin K, e.g. green vegetables or milk, was completely absent; or when one or more factors were seriously deficient.

A history of adequate diet (as defined) was obtained from 24 mothers whose babies were examined during the first few days of life. In 19 of these cases, delivery took place in the late summer or autumn. All deliveries except one (by the low forceps) were spontaneous. In one only of the babies did any cerebral symptoms occur and in no case was there any spontaneous bleeding. The mean of the daily prothrombin index has been plotted as a curve (Fig. 1A). During the first 12 hours of life, the mean prothrombin index exceeds 80 per cent, a reading which would be a low normal for an adult. Thereafter, a fall in the index during the first 3 days of life to just below 65 per cent is followed by a rapid return towards normal.

On the same figure are drawn:

1. The average daily prothrombin index of 54 consecutive patients in whom the dietetic history was not investigated (Fig. 1B). Forty-four of these were delivered spontaneously with the vertex presenting, in 3 the presentation was a breech and 7 were delivered by the forceps. Compared with the values of the prothrombin index when the mother's diet has been adequate, the curve of this series starts at a lower figure, and runs parallel at about 10 per cent lower during the first 3 days of life. Subsequently it returns more slowly towards normal.

2. The mean of the prothrombin index of 9 babies whose

mothers gave a history of gross dietary deficiency (as defined) during pregnancy, but did not show any evidence of toxaemia or other important systemic abnormality (Fig. 1C). Comparison with the other 2 curves in Fig. 1 demonstrates that in these circumstances the prothrombin index is very low even within 24 hours of birth and remains low for an unusually long time. The maternal prothrombin index averaged 87 per cent and was

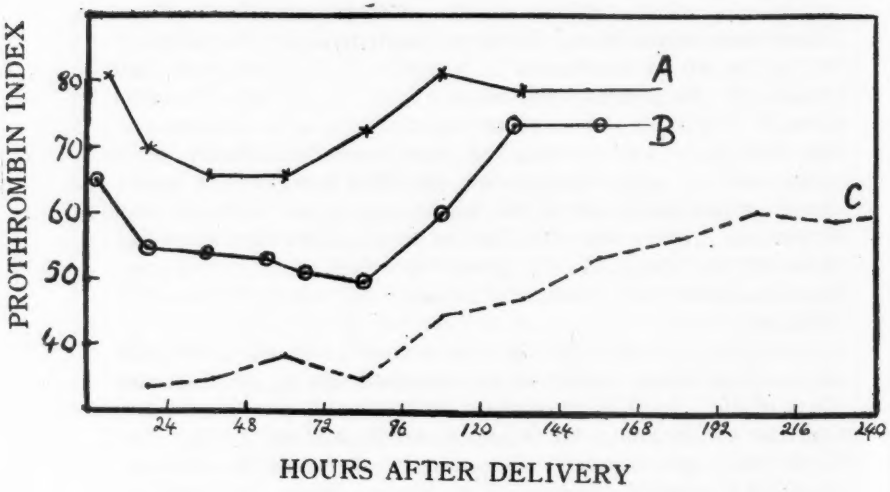


FIG. 1

A—Adequate diet. B—Control series. C—Deficient diet.

below normal adult levels in 1 case only (70 per cent). Clinically, symptoms of cerebral irritation developed in 3 of the babies, (in 2 of which symptoms suggested and necropsy subsequently confirmed that fresh bleeding had occurred late on the 2nd day), and there were 6 cases of haemorrhagic disease, all of which began within the first 4 days of life, at the time when the prothrombin deficiency was greatest.

(2) *Toxaemia*

The appearance of a persistent rise in blood-pressure above 130/80, of albuminuria which could not be traced to benign or infective causes, and of oedema in association with either or both of these findings, was taken as the criterion for diagnosis of preg-

nancy toxaemia. Toxaemia has been graded according to the severity of these and of certain other symptoms (Table II). The classification of each case is determined by the intensity of the predominant symptoms at the worst period of the illness. While such a simple method of gradation is necessarily incomplete, it is believed that it is sufficiently representative for the purpose of correlating the severity of the illness with variations in the prothrombin index in the new-born. The effect of the duration of the toxaemia before termination of pregnancy was also examined, and patients who had been ill for more and for less than 5 weeks (the figure quoted by Browne and Dodds[18] as the mean for 71 patients who became well) have been studied separately.

The results obtained in 37 consecutive cases of pregnancy toxaemia (deliveries of 18 of the patients being instrumental or by the breech, and 4 by Caesarean section) show that the initial values of the prothrombin index and the fall during the first 4 days of life correspond with those of the control series, but that the subsequent recovery is delayed, the normal level for infancy being reached only on the 8th day (Table III). The prothrombin index of the 18 babies delivered instrumentally or by the breech shows little variation from the mean values of the whole series. Moreover, in this small series the incidence of complications which may arise as a result of hypoprothrombinaemia (Table IV) suggests that the trauma of delivery does not greatly influence the extent of the prothrombin deficiency, but, when this is already present, may aggravate symptoms which might otherwise have remained latent.

Comparison of the curves obtained for the 3 degrees of toxaemia (as defined above) shows that there is no correlation between the severity of the illness in the mother and the extent of the prothrombin deficiency in the infant (Table III). The duration of the illness, however, does seem to affect the prothrombin index in the infant, the average curve obtained in patients in whom toxaemia has been present for more than 5 weeks showing a greater deficiency and a slower return towards normal. Even so, in the individual case this effect is not constant, suggesting that this is not the only factor concerned. Further, in none of the babies born of mothers whose toxaemia had been prolonged did any cerebral symptoms develop, and in only one was there spontaneous bleeding, whereas after an illness lasting less than 5 weeks there were 6 babies with cerebral symptoms and 3 with haemorrhagic disease.

It appears, therefore, that pregnancy toxaemia itself influences the degree of neonatal hypoprothrombinaemia slightly only; that there is no relation between the severity of the toxaemia and the degree of prothrombin deficiency; and that while, on the average, prolonged toxaemia is followed by an increased deficiency and a slower recovery rate in the prothrombin index, there is, in this series, no correlation between the duration of the illness and the incidence of complications commonly associated with hypoprothrombinaemia in the new-born.

Analysis according to the history obtained of the diet during

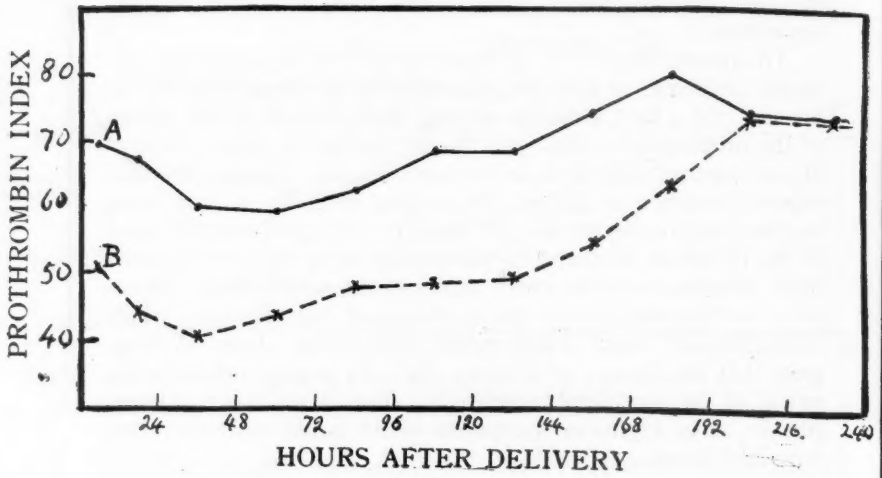


FIG. 2

A—Toxaemia, diet adequate. B—Toxaemia, diet deficient.

pregnancy showed that diet had been adequate in 18 cases (20 babies) and deficient in 16 (17 babies). Comparison of the results obtained in the 2 groups (Fig. 2) reveals that:

1. When diet has been adequate during pregnancy, the prothrombin index differs from that found under the same conditions in healthy mothers only in that the minimal value is a little lower and the recovery rate a little less rapid.

2. When the mother's diet has not been adequate, a very great increase in the prothrombin deficiency results and the delay in restoration is so marked that the prothrombin index

remains below 50 per cent on the 6th day of life and does not approach normal figures till the 9th day.

3. There is no significant difference in the maternal prothrombin index—diet adequate 91; diet deficient 87.

4. Whereas the mortality and the incidence of cerebral symptoms are the same (1 and 3 respectively) in the 2 groups, haemorrhagic disease developed in 4 babies after a deficient dietary regimen during pregnancy, but did not occur when the diet had been adequate.

(3) *Prematurity*

A birth weight of less than $5\frac{1}{2}$ pounds has been accepted as the standard of prematurity.

The daily mean of the repeated prothrombin estimations made on 36 premature infants has peen plotted in Fig. 3B. The

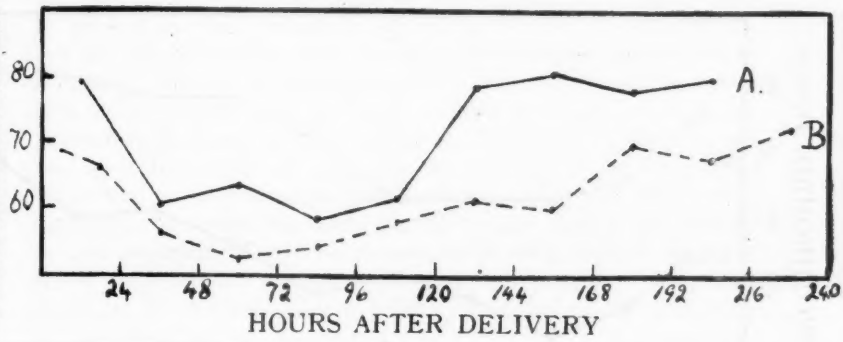


FIG. 3

A—Seven cases of premature delivery with toxaemia and adequate diet in pregnancy. B—Thirty-six cases of premature births.

index chart forms a curve which closely resembles that of the control series (Fig. 1B) during the first 5 days, but in which the recovery towards normal is slower. The curve does not correspond, however, either with the gross deficiency of prothrombin described by Hellman and Shettles[19] in the premature infant, or with the high values which have been found by Waddell and Lawson.[20] The discrepancy between the results of these workers has been ascribed to difference in technique and taken to indicate that the ease with which the prothrombin in the premature is converted into thrombin compensates for its gross quantitative deficiency. But, as the method used in this investigation is

essentially the same as that of Quick (used by Waddell) and has been found to give comparable results, this assumption cannot explain the dissimilarity between the present series and those of the American workers. Further analysis has, therefore, been made.

1. In 18 cases there was no history of dietary deficiency in the mother, and abnormal features did not develop in the neonatal period. Four babies subsequently died (epidemic gastroenteritis 3, "premature" 1) but in no instance did any cerebral symptoms or spontaneous bleeding occur. There is a notable similarity in the prothrombin index charts obtained in the premature (Fig. 4A) and the mature babies (Fig. 1A) of adequately nourished mothers. During the first 3 days of life the curves are almost identical, but there is a lag in the onset of the subsequent recovery towards normal in the premature series.

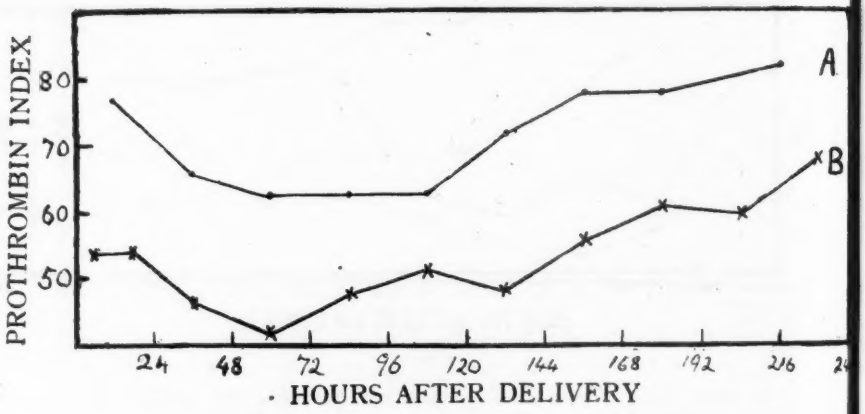


FIG. 4

A—Eighteen cases of premature delivery with adequate diet in pregnancy.
B—Seventeen cases of premature delivery with deficient diet in pregnancy.

2. Seventeen babies were born of 15 mothers, from whom was obtained a history of dietary deficiency during pregnancy. Of these, 9 were also toxaemic, 1 (the mother of twins) had had persistent nausea and occasional sickness associated with pyelitis, and in 1 (also a twin pregnancy) who did not show any toxaemic symptoms and had a prothrombin index of 97, labour had to be induced for an external accidental haemorrhage during (reputedly) the 35th week. Seven deaths occurred in the neonatal period, in 6 of which the cause of death

was found to be atelectasis 1; cerebral haemorrhage 2; secondary hepatic dysfunction 1; gastro-enteritis 2. There were 5 cases of haemorrhagic disease, 2 on the 2nd, and 1 each on the 3rd, 4th and 7th days of life. The mean of the daily prothrombin index forms a curve (Fig. 4B) which falls to a level considerably lower than when the diet in pregnancy has been adequate and returns to normal levels more slowly. The initial and the minimal values are, however, higher than those found in mature babies of inadequately nourished mothers. This may be related to the fact that pregnancy has been curtailed and hence probably the duration of dietary deficiency has been shorter and its degree relative to the foetus less severe.

It appears, therefore, from a study of the corresponding curves in mature and premature babies (Fig. 1A and C, Fig. 4A and B) that the clotting activity of the blood as measured in terms of the prothrombin index by this method is not significantly altered in the premature infant by reason of prematurity *per se*. Nevertheless, while the processes involved in the metabolism of vitamin K—absorption from the intestine and conversion to prothrombin in the liver—appear to be as active in the premature in restoring the clotting activity of the blood to normal as in the infant at term, yet the inability of the premature organism (with its smaller blood volume and hence lower total circulating prothrombin unsupported by any reserve of vitamin K and maintained only by a very small milk intake) to withstand abnormalities of these processes which would cause little upset in the mature baby can be appreciated in the following 2 case records (Fig. 5).

(1) 5905. Birth weight 3¼ pounds. Classical Caesarean section for severe (Grade 3) pre-eclamptic toxaemia. Diet—green vegetables about twice a week; milk ½ pint a day; meat adequate; fats ? adequate. Maternal prothrombin index 90. Condition at birth fairly good. Progress—Accidental incision on back which was stitched and healed by primary union. No bowel movement and vomited after every feed during first 3 days of life.

Half-and-half breast milk and water 2-hourly. Transient jaundice 3 to 6 days. Developed boil on buttock which had to be incised on the 7th day. During this time there was a secondary fall in the prothrombin index of nearly 20 per cent. Subsequent recovery in the prothrombin index and the clinical course were normal.

(2) 6033. Birth weight 5 pounds. Spontaneous vertex delivery (the first of twins). 17 hours labour. Mother—Grade 2 pre-eclamptic toxaemia. Diet—green vegetables deficient (in soups only about twice a week). Meat deficient; milk and fats satisfactory. Progress—Breast feeding with supplementary

glucose saline. Normal course till 9th day when epidemic gastro-enteritis developed. No jaundice. Laevulose tolerance test normal (Thomson and Wilkinson[21]).

Died on 15th day. Necropsy disclosed a normal liver and inflammation of the stomach and jejunum.

In two other cases of gastro-enteritis and in many cases of parenteral infection in mature infants, the prothrombin index has been found to be within the normal limits for the age of the child.

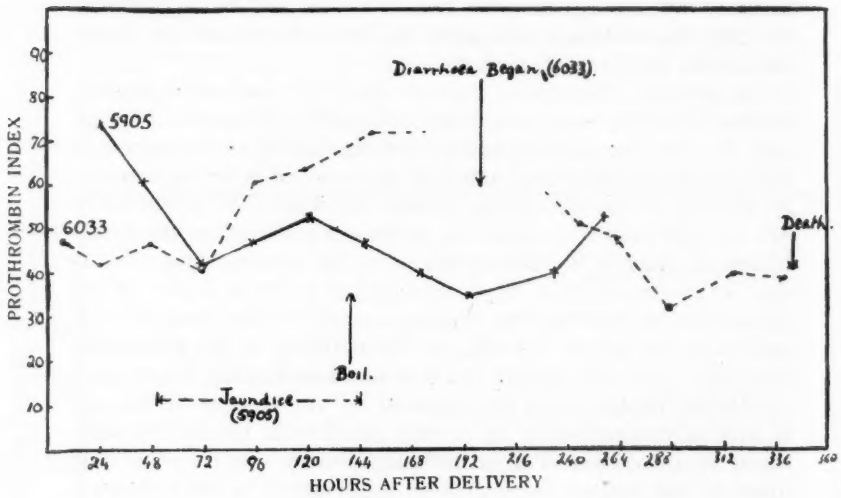


FIG. 5

3. Five mothers who gave a history of adequate antenatal diet suffered from toxaemias of pregnancy. The chart of the mean daily prothrombin index obtained in these 7 babies (Fig. 3A) indicates that in the premature infant also the prothrombin index is not affected by pregnancy toxaemia alone. In none of these cases did any cerebral or haemorrhagic symptoms occur.

(4) *Prolonged Labour*

From the material used in this investigation, 18 cases of prolonged labour (more than 36 hours duration) were selected and were divided into 2 groups: Group A, in which anaesthesia had been used only for delivery (14 cases); and Group B, when more than one inhalation anaesthetic had been given during labour (4 cases).

In group A, 3 mothers had a history of dietary deficiency during pregnancy; there were 6 spontaneous and 8 abnormal deliveries (including one Caesarean section after prolonged trial labour); and 2 deliveries by the forceps developed cerebral

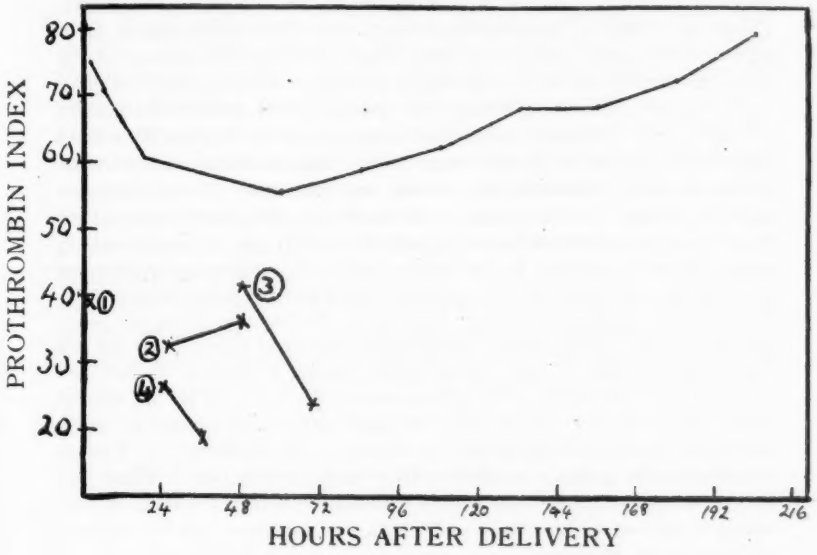


FIG. 6
Prolonged labour. Numbers as in text (Group B)
Curve of cases in Group A.

symptoms during the first 24 hours after birth, which subsided spontaneously. There was no case of haemorrhagic disease. The curve formed by the prothrombin estimations of the whole group (Fig. 6) did not show any abnormal deficiency; and those of the spontaneous and abnormal deliveries differ only in the lower values (about 10 per cent lower) found in the latter on the 2nd and 3rd days. This suggests that prolonged labour *per se*, even when terminated instrumentally, does not have a significant adverse effect upon the prothrombin index during the first few days of life.

In group B, the records of the 4 cases are (Fig. 6):

(1) 1004/39. In-patient (hyperemesis gravidarum) for 6 weeks during 3rd and 4th months of pregnancy. Developed Grade 2 pre-eclamptic toxaemia. Medical induction followed by 52 hours labour. Left occipito-posterior position.

Chloroform and oxygen used for manual rotation 12 hours before delivery, and for delivery by the forceps. Asphyxia livida at birth and extremely restless for some hours after. Vitamin K analogue given early as the prothrombin level of the blood of the umbilical cord was unusually low (39 per cent).

(2) 5024/40. Antenatal diet adequate. Labour 37 hours. Right occipito-posterior position. Manual rotation under anaesthesia (chloroform and oxygen) 9 hours before delivery. Spontaneous delivery under chloroform analgesia. Baby limp at birth; facial paresis; responded slowly; prothrombin index 32; developed very marked cerebral symptoms on 3rd day for which an injection of 2.5 mgm. of 2–methyl–1, 4–naphthoquinone was given with considerable benefit.

(3) 6633/40. Chronic cholecystitis for which a low fat diet was being taken under supervision of the dietetic department. Disproportion suspected. Examination under chloroform anaesthesia 21st Feb., 1941. Two attempts at quinine-pituitary induction made on the 23rd and 24th. Second examination under anaesthesia (chloroform and oxygen) Feb. 28th, 1941. Labour lasted 115 hours and was completed by the forceps mid-cavity under gas, oxygen and ether. Baby very limp at birth; wakeful, crying and twitching subsequently. Persistent ooze from heel puncture on 3rd day. Prothrombin index 24. Injection of 2.5 mgm. of K-analogue arrested the superficial bleeding but did not lead to any immediate improvement of the cerebral symptoms. Mother died on 6th day of puerperium. The post-mortem report (Dr. A. M. Macdonald) reads " great damage to liver cells. Necrosis, atrophy and extreme vacuolisation all present with apparently no attempt at regeneration . . . There is considerable bile pigment retained in these damaged liver cells." Baby died from epidemic gastro-enteritis on the 23rd day. Necropsy showed the remains of subdural haemorrhage under both parietal bones, but no evidence of intracerebral bleeding.

(4) 7252/41. No illness in pregnancy. Diet deficient—green vegetables approximately once a week; milk ½ pint a day. Maternal prothrombin index 82. Labour 76½ hours. Right occipito-posterior position. Chloroform and oxygen anaesthesia used for (1) examination 20 hours before delivery (light); (2) manual rotation 15 hours before; (3) delivery by the forceps. Baby limp at birth, responded quickly. Copious haematemesis early on the 2nd day of life. Stomach wash-out showed frank blood. Bled from heel-stab for 13 hours, eventually stopped following an injection of 2–methyl–1; 4–naphthohydroquinone disuccinate after the mother's blood had failed to arrest it.

The prothrombin estimations obtained before K-analogue was administered to these infants are abnormally low and present a marked contrast to the mean values in group A. In 3 cases the infants had severe cerebral symptoms and in 2 cases a manifest haemorrhagic disease. The hepato-toxic effect of chloroform with a resultant rapid failure of prothrombin formation has been clearly demonstrated in animals by Smith[22] *et al.* and by other workers. In case 6633 (the most severe in group B), the co-incidence of prolonged labour and 3 inhalation anaes-

thetics (of which the two before delivery were both chloroform) with gross liver damage in the mother and profound hypoprothrombinaemia in the baby is very striking. It appears that in the presence of factors in pregnancy or labour, not in themselves necessarily adverse to the health of mother or child, chloroform may be dangerous in a way that has not previously been suspected. The mechanism of this action is not immediately clear. Prothrombin synthesis is believed to occur in the foetus from the vitamin K radicle which passes unchanged through the placenta. Hence the depressant action of repeated anaesthesia with chloroform upon the neonatal prothrombin is probably a sequel not so much to the hepato-toxic effect in the mother as to a direct and similar action upon the liver of the foetus. Sheehan[23] has shown that the likelihood of toxic action by chloroform is least in the well-fed mother and greatest when maternal reserves are exhausted by malnutrition, vomiting or prolonged labour. It seems reasonable to assume that these same conditions will drain foetal reserves to an extent which may expose the foetus to the same risks as the mother. If the foetal liver, already handicapped in the formation of prothrombin by lack of vitamin K, is further impeded by imprudent administration of chloroform, the earliest and possibly the only evidence of any toxic effect is likely to be profound neonatal hypoprothrombinaemia.

(5) *Neonatal Causes of Prothrombin Deficiency*

The deficiency of vitamin K in the diet of the new-born, the low absorption of fats from the alimentary canal and the sterility of the intestinal contents (Quick and Grossman, Grossman, and others) have all been stressed in the causation of neonatal hypoprothrombinaemia and haemorrhage. In an attempt to evaluate the *rôle* of such factors, 4 hydrocephalic babies who had been pronounced inoperable by the Neurosurgical Unit, were fed on a diet of glucose saline or glucose water only. No other accessory food substances were given. Diet excepted, the treatment of these cases was identical with that of other babies in the nursery. In 3 of them the case records are complete for mother and baby; the 4th was born outside the hospital and an opportunity of questioning the mother has not arisen. The prothrombin index charts are shown in Figs. 7-10.

(1) 4797/40. No record of mother obtained. Spontaneous vertex delivery, 6½ pounds. Birth condition reported to be satisfactory. Glucose saline feeds only.

Progress:

Day 2. Regurgitant vomiting which persisted till day 8.
Day 4. Stools scanty, loose, green.
Day 7. Clinical oedema appeared. Gradually increased.
Day 13. Death at 289 hours.

Faecal organisms (post-mortem specimen)—" a few acidophilus bacilli, few enterococci, many *b.* coli."

Post-mortem examination—gross hydrocephalus and uninfected myelomeningocele. No sign of bleeding, of intestinal inflammation or of abnormalities in liver, spleen or kidneys.

(2) 5923/41. Spontaneous vertex delivery in para 3. Four-hour labour. Birth weight 8¼ pounds. Maternal diet deficient—green vegetables not more than twice a week; milk ½ pint a day; other fats doubtful; meat 4 or 5 times a week. Prothrombin index 90.

Progress:

Day 1. Glucose saline 3-hourly.
Day 4. Clinical oedema appeared and rapidly increased.
Day 6. Scanty loose greenish stools (2 or 3 a day). Similar motions continued for remainder of life.
Day 7. Red blood corpuscles 6 millions, haemoglobin 145. Slight jaundice.
Day 8. Weight 9 pounds. Gross oedema. Glucose water feed.
Day 11. Weight 8¼ pounds. No clinical oedema. Bleeding time 5 minutes. Clotting time 3 minutes.
Day 17. Vomiting began. Bleeding time more than 10 minutes. Clotting time 4 minutes.
Day 21. Baby died from acute respiratory failure.

Post-mortem examination—Large internal hydrocephalus and broken myelo-meningocele in dorso-lumbar region. Alimentary canal and liver normal. No evidence of bleeding.

(3) 6236/41. Caesarean section after 9 hours trial labour in para 1 (stillborn) with double uterus. Birth weight 5 pounds. Maternal condition—no toxaemia; iron-deficiency anaemia (red blood corpuscles 3½ million, haemoglobin 45); diet in pregnancy full and adequate. Prothrombin index 93. Glucose water feeds 3-hourly.

Progress:

Day 4. Red blood corpuscles 5½ million, haemoglobin 120.
Day 5. Weight 4 pounds.
Day 7. Scanty loose green-yellow stools, 1 to 3 a day.
Day 9. Faecal organisms—staphylococci and enterococci predominate. *B.* coli scanty. General condition apparently healthy.
Day 16. Laevulose tolerance test normal.
Day 18. Red blood corpuscles 5 million, haemoglobin 90.
Day 19. Faecal organisms—as in previous examination. Vomiting began.

Day 20. Died from circulatory and respiratory failure.

Post-mortem report—Internal hydrocephalus and lumbar meningocele. No abnormality of liver or intestinal tract. No evidence of bleeding.

(4) 6887/41. Spontaneous vertex delivery, 10 hours labour, 5¾ pounds. Maternal condition—pre-eclamptic toxaemia Grade 2; diet in pregnancy deficient—green vegetables "occasionally only," milk none except in puddings and in tea, meat about 4 times a week. Prothrombin index 87.

Progress:

Day 1. Glucose water 3-hourly. Bleeding time 4 minutes. Clotting time 2½ minutes.

Day 5. Five scanty loose stools. Clotting time 3 minutes.

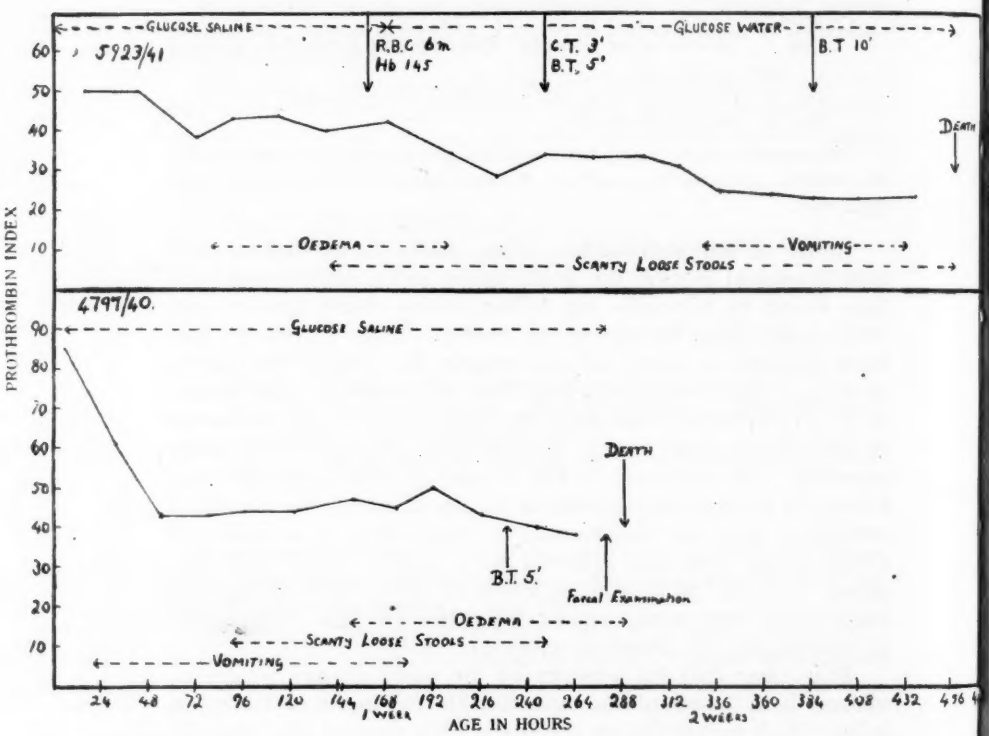
Day 6. Died at 111 hours.

Post-mortem report—Large hydrocephalus and dorso-lumbar meningocele. No evidence of internal haemorrhage. No abnormality of liver or gastro-intestinal tract.

Study of the prothrombin index charts shows that in each case the initial drop in the prothrombin index corresponds with that found in normally fed babies, being much greater and more rapid when the diet of the mother during pregnancy had been deficient in foods rich in vitamin K. When the diet in pregnancy had been satisfactory there was a steady slow decline in the prothrombin index from the birth value of approximately 90 per cent to 48 per cent at the end of the 3rd week when death occurred. By contrast, in the 2 cases in which the diet was known to be inadequate (and in 1 case in which the antenatal conditions were not discovered), a rapid drop to an index of about 40 per cent was followed by a plateau which fell very slowly to reach (in case 5923) levels at which the bleeding and coagulation times were considerably prolonged (the "subclinical haemorrhage" of American authors).

It is clear that the absence of the usual dietary source of vitamin K in the infant does not affect the fall in the prothrombin index which occurs during the first 2 or 3 days of life. On the other hand, it is reasonable to associate the non-appearance of the subsequent restoration towards normal with the feeding given. Moreover, while the rapidity of the fall was checked in cases 4797, 5923 and 6887, yet the prothrombin index continued to fall slowly despite the presence of K-forming organisms in the intestinal tract. The stools were loose, scanty and infrequent, as would be expected from such a low residue diet, but true diarrhoea did not occur to interfere with intestinal absorption. The persistence of the fall in the prothrombin index suggests that, in the absence of a dietary source, the bacteria present in

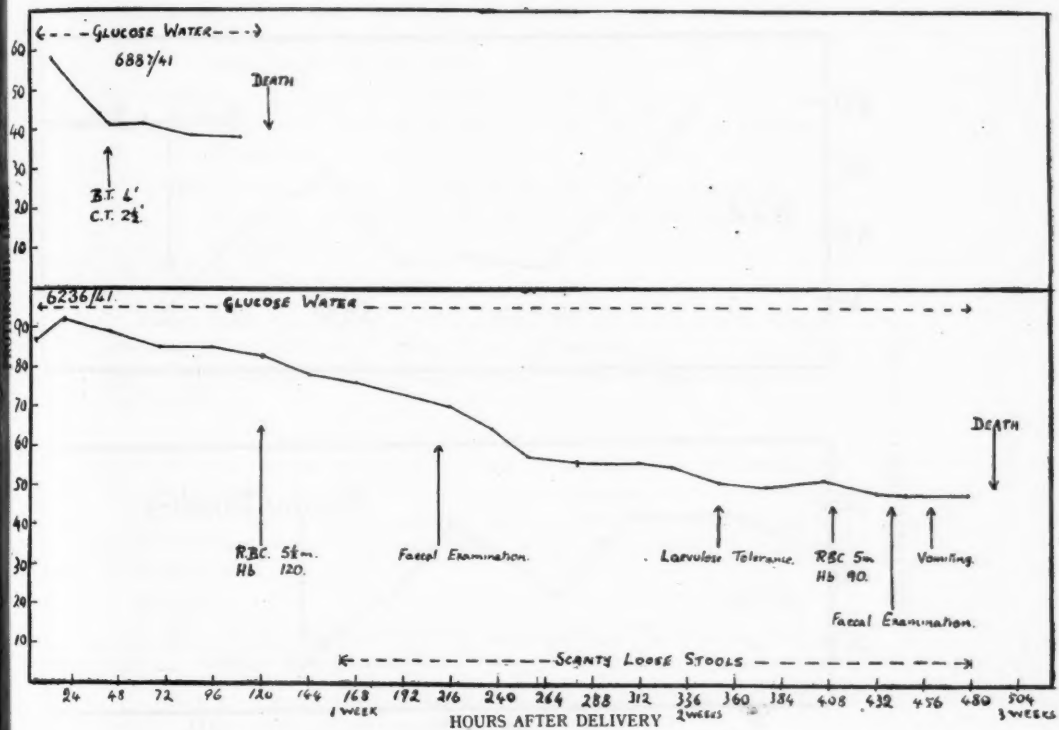
the alimentary canal cannot provide a supply of vitamin K sufficient to balance the normal physiological destruction of prothrombin. It would appear, therefore, that the importance attached by Quick and Grossman to the synthesis and absorption of vitamin K which follow bacterial invasion of the intestine in the new-born is exaggerated. It is noteworthy, however, that this



FIGS. 7 AND 8

supply of vitamin K was sufficient to maintain clot formation and to prevent spontaneous bleeding after the 10th day of life at levels of the prothrombin index which in the new-born are usually associated with the onset of haemorrhagic disease. This observation may be correlated, firstly, with the fact that the fall in the prothrombin index which precedes the occurrence of haemorrhage in the new-born is so rapid that there may not be time for the development of compensatory mechanisms; and

secondly, with the experience of Greaves[24] who found that prolonged feeding on a vitamin K-free diet led to a marked prothrombin deficiency in only 15 out of 77 rats, and did not *per se*



FIGS. 9 AND 10

give rise to spontaneous bleeding in any. Almquist and Stockstad[25] too have demonstrated the importance of vitamin K reserves in increasing the resistance of chickens to haemorrhagic disease when a diet rich in alfalfa had been fed to the hen. That entirely comparable effects pertain in the human is evident on examination of the prothrombin index charts in these cases. When the antenatal diet of the mother had been full and adequate, the prothrombin index in the infant did not fall so low at the end of 3 weeks as it did in 3 days in the offspring of mothers whose diet had been deficient.

It is probable, therefore, that serious prothrombin deficiency after the first 4 days of life will be rare and will be encountered only when more than one prejudicial factor is acting simultaneously. In only 5 cases in this series has this occurred. Two of

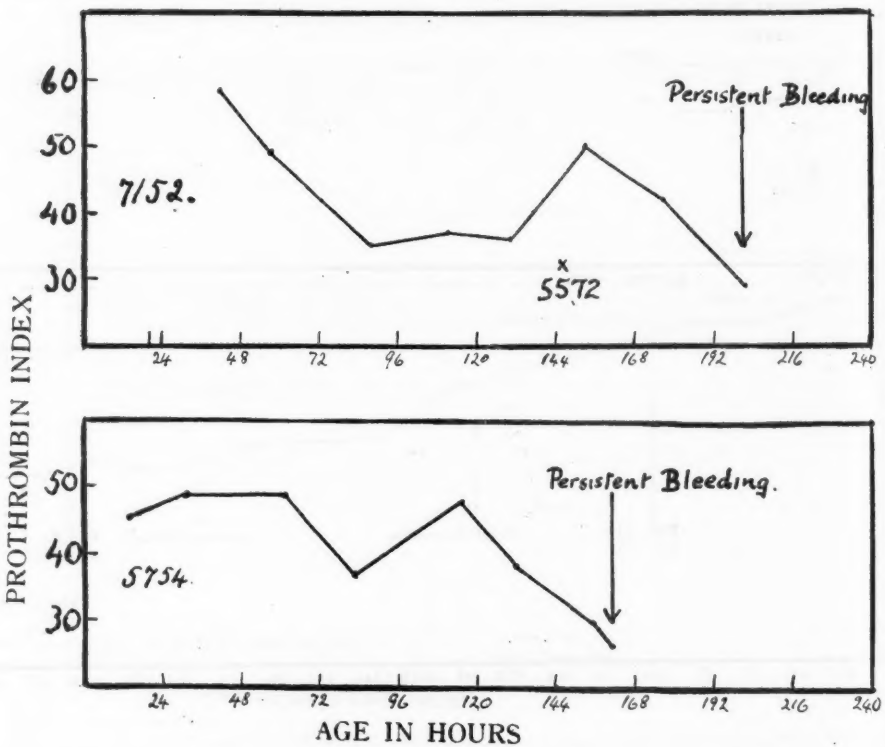


FIG. 11

these have already been cited (Fig. 5). The records of the others follow (Fig. 11):

(1) 5572/40. Spontaneous vertex, 6½ pounds. Maternal dietary history unknown. Oesophageal atresia. Subcutaneous salines only. Prothrombin index on 7th day, 32 per cent. Gastrostomy on 8th day followed by massive and fatal mediastinal haemorrhage.

(2) 5754/40. Spontaneous vertex, 4¼ pounds, 10 hours labour. Maternal condition—pre-eclamptic toxaemia Grade 3; diet—grossly deficient; had been

put by her general practitioner on to a meatless, salt-free diet, but refused to take any vegetables without salt; milk, ½ pint a day. Prothrombin index 95.5.

Progress—Birth condition fairly good.

Day 4. Clinical jaundice appeared and steadily deepened. Faeces pale.

Day 7. Persistent bleeding from heel-stab. Prompt and maintained response to intramuscular injection of 5 mgm. 2-methyl-1, 4-naphthohydroquinone disuccinate.

Day 9. Laevulose tolerance test—30 minutes, 6 mgm.; 60 minutes, 6 mgm.; 120 minutes, 7 mgm. per cent (? = delayed intestinal absorption.)

Day 10. Icteric index 333. Van den Bergh—Prompt biphasic. Faecal fats—total 33.7 per cent, split 29.7 per cent of total (i.e. failure of fat digestion).

Day 12. Died at 265 hours.

Post-mortem examination revealed a distended gall-bladder and a deeply bile-stained liver and kidney cortex. There was remarkably little necrosis in either organ, however. Probably the cause of death was secondary hepatic dysfunction.

(3) 7152/41. Spontaneous vertex, 5½ pounds, 6 hours labour in para 2. Both previous children jaundiced, of whom the second died. Hypertension for which hospital treatment for 6 weeks before delivery. Diet—green vegetables, a little daily; milk, ½-1 pint a day; no meat. Laevulose tolerance, plasma proteins and serum calcium normal. Prothrombin index 83. Erythroblastosis foetalis.

Progress:

Day 3. Clotting time 2 minutes, haemoglobin 90, reticulocytes 26 per cent.* Icteric index 200.

Day 5. Clotting time 3½ minutes, bleeding time 6½ minutes, haemoglobin 90, reticulocytes 28 per cent.

Day 8. Faecal examination—*b.* acidophilus, *b.* coli (lactis aerogenes) and a few enterococci, normal flora. Bleeding time 7 minutes. Clotting time 4 minutes, haemoglobin 75, reticulocytes 12 per cent.

Day 9. Haemoglobin 66, reticulocytes 8 per cent. Laevulose tolerance test (30 minutes, 17; 60 minutes, 12.5; 120 minutes, 12 mgm. per cent) suggested delayed metabolism by the liver.

Persistent oozing occurred from heel-stab with clotting time of 6 minutes and prothrombin index 29. Prompt and maintained response to intramuscular injection of 2.5 mgm. of 2-methyl-1, 4-naphthoquinone, despite the following findings subsequently:

*The haemoglobin and reticulocyte estimations were done by Dr. J. L. Henderson.

(1) Haemoglobin and reticulocyte readings fell 2 days later to 50 and 60 per cent respectively. 75 c.c. packed red blood corpuscle transfusion given without further effect on clotting activity. On day 17, haemoglobin had again fallen to 42 and a second similar transfusion had to be given.

(2) Laevulose tolerance tests—on day 15 still showed deficient hepatic function (30 minutes 10; 60 minutes 17.5; 120 minutes 7.5 mgm. per cent). One week later test was normal.

(6) *Haemorrhage in the New-born*

In 13 cases of haemorrhagic disease and in 2 cases of erythroblastosis foetalis in which spontaneous haemorrhages occurred prothrombin estimations have been made as soon as possible after the onset of bleeding. Details of these cases are set out in Table V, from examination of which the following points emerge:

1. The most frequent site of bleeding is the alimentary canal. Bleeding only occurred once in this series from other mucous surfaces and haematuria was not observed. Miller[26] has recently pointed out the frequent occurrence of gastric hyperacidity immediately after birth. To link this observation with the preponderance of alimentary over other types of bleeding and to suggest that peptic ulceration is more common immediately after birth than has been believed hitherto assumes that relations similar to those in the adult prevail in the new-born between the gastric secretion and the gastric mucosa—an assumption which appears to be in agreement with Miller's histological findings. Massive haemorrhage from a duodenal ulcer was proved post-mortem in one baby (not included in this series as a prothrombin estimation was not made) whose bleeding and coagulation times were prolonged, but in no other case did the opportunity for examination arise. It was noted, however, that with treatment which invariably stopped superficial bleeding in under 3 hours, melaena persisted for 12 to 24 hours, a fact which suggests a bleeding point high in the intestinal tract.

2. Intracranial haemorrhage was found at necropsy in 4 cases, in all of which cerebral symptoms had been pronounced and persistent bleeding from other sites had occurred. Cases 6912 and 6913 (twins) provide a striking example of the exacerbation of traumatic bleeding by abnormal prothrombin deficiency. In both cases external and intra-cerebral bleeding occurred. In case 6912 large haemorrhages were also found in the lungs, liver and suprarenals.

3. In every case the prothrombin index was abnormally low, the actual value varying between 18 and 38 per cent. This observation agrees with those recorded by other authors. But, while every baby with such a low clotting activity is a potential bleeder, in one case in this series, in which severe prothrombin deficiency was found, abnormal bleeding did not occur.

Case 5568/40. Delivery by the low forceps after 28 hours labour. Birth weight 6¾ pounds. Prothrombin index—37 hours after birth, 22.8; 45 hours 16; 61 hours 32.7; 90 hours 51.7 per cent. No abnormal bleeding recorded.

As the same methods of obtaining blood and of observing bleeding times were used in all cases, it is clear that trauma cannot be the only factor which determines the onset of bleeding at low prothrombin levels. In the case recorded, the rise in the prothrombin index to "safe" values in a comparatively short space of time shows that there was effective absorption of vitamin K and synthesis of prothrombin, certainly after 45 hours of age. Whether these processes were sufficiently active before this time to prevent abnormal bleeding, or whether some other factor such as unusual capillary tone was operating, could not be determined at the time of investigation.

4. The onset of persistent bleeding was within the first 4 days of life in 12 of the 15 cases. In none of these infants (with the exception of 4 who had cerebral symptoms) was any pathological feature other than profound hypoprothrombinaemia discovered. As has been noted above, prothrombin deficiency sufficiently great to be a cause of haemorrhage only occurs after this time if liver function is seriously impaired (as it may be in erythroblastosis) or when two or more factors each adversely affecting vitamin K metabolism occur simultaneously (case 5572—operation in a case of complete failure of ingestion; case 5754—obstructive jaundice and partial liver failure superimposed on vitamin K reserves depleted by maternal dietary deficiency).

5. Only 3 babies (delivered from 2 mothers) were premature, and in every case other more definite predisposing factors were present. In one case the bleeding began in a week-old baby. In the twins, cerebral haemorrhage also occurred.

As far as can be judged from so small a series, prematurity *per se* does not tend to increase the frequency of haemorrhagic complications. That all the infants died, however, serves to emphasize the gravity of the condition in the premature.

6. Pregnancy had been complicated by true pre-eclamptic

toxaemia in 1 case and by hypertension in 4. In 3 cases symptoms had been of such duration or so progressive as to require termination of pregnancy, but in one case only was toxaemia the sole antenatal predisposing factor. This (7152) was a case of erythroblastosis foetalis.

7. The conditions of labour and delivery (including one Caesarean section of election) bear no relation to the occurrence of bleeding. In 3 cases (6446, 6633, and 7252) the abnormality of labour has been imposed upon a pre-existing condition. In the first, a short hard labour and the pressure of the umbilical cord tightly wound round the neck caused capillary damage and bleeding in a case of erythroblastosis foetalis. (Javert[27] describes 3 similar cases of "intra-uterine" bleeding, in each of which short hard labours occurred in patients who had had an antenatal abnormality.) The complicated labours of women whose vitamin K reserves were already depleted (6033, 7252) have been described.

8. In only 2 of the 11 mothers (12 babies) whose diet in pregnancy has been investigated has gross deficiency in the intake of foods rich in vitamin K not been found. All patients delivered prematurely and suffering from pregnancy toxaemia whose children developed haemorrhagic disease also gave a history of dietary deficiency during pregnancy. Deficient diet was the only abnormality discovered in 3 cases (4 babies); in 2 others, the effects of a restricted diet were accentuated by complicated labours or by conditions which tended to reduce the absorption of vitamin K from the intestine (case 6633). Erythroblastosis foetalis (icterus gravis) was present at birth in the offspring of both those mothers whose dietetic history did not show a grossly deficient consumption of milk and green vegetables. Thus, if these 2 cases be set aside—for the erythroblastosis appears to be the primary condition of which prothrombin deficiency and haemorrhagic tendencies may be complications—it is apparent that in every case of true haemorrhagic disease in which it was possible to question the mother about her antenatal habits, there was a history of grossly deficient consumption of foods rich in vitamin K.

Furthermore, the incidence of haemorrhagic disease in the Simpson Memorial Pavilion during the winter and spring months of 1940-41 (0.85 per cent) is almost exactly 4 times the incidence reported for the year 1939 (0.21 per cent)[28]. This increased incidence in and after a particularly hard winter during which there was a prolonged and widespread scarcity of green vegetables of

all kinds, appears to substantiate the evidence presented above in individual cases, and may reasonably be ascribed to the enforced lower consumption of protective foods throughout the country, and especially by the poorer sections of the population.

Discussion

The bulk of recent research upon the haemorrhagic state in the new-born has been concerned with the demonstration of the associated extreme prothrombin deficiency and of the beneficial effect of vitamin K therapy, but has paid little attention to factors which predispose to this condition. Kugelmass was the first to discuss the use of diet in the prevention of bleeding and to describe prophylaxis against neonatal haemorrhagic disease by the administration of a diet rich in proteins, fats and vegetables to the mother. At that time (before the natural sources or clinical applications of vitamin K were known) he believed the protein constituents to be the active factor, but it seems probable, in the light of more recent investigations, that the success of his dietary regimen was due to the consumption of milk thrice and vegetables twice in the day. In the present series the co-existence of abnormal prothrombin deficiency in the new-born and of low intake of food substances rich in vitamin K by the mother is too constant to be fortuitous. Moreover, this dietary deficiency remains the one common factor in patients who differ widely in their prenatal health, the nature of their labour and the manner of their delivery, and is most pronounced in those mothers whose offspring developed haemorrhagic symptoms. Mechanical factors may determine the site of haemorrhage but appear to play only a small part in its incidence. Similarly there is no clear evidence that toxaemia or prematurity predisposes to the development of severe prothrombin deficiency, though prematurity may affect the prognosis. It is noteworthy that the maternal prothrombin index remained constantly within the limits of normal, irrespective of the vitamin K consumption during pregnancy. In 2 cases only did it fall below 80 per cent. This observation falls into line with those of Kark and Lozner[29] and of Scarborough[30] who found that dietary deficiency of vitamin K in the adult only caused a minor degree of hypoprothrombinaemia and that only when the K-deficient dietary had been prolonged and was associated with other gross deficiency syndromes. It appears that when the consumption of foods rich in vitamin K is low during pregnancy the absorption from the

alimentary canal is sufficient to maintain a normal concentration of prothrombin in the mother's blood, but fails to prevent so serious a depletion of the vitamin K reserves that practically none is available for storage or even synthesis into prothrombin in the foetus. Other factors may be concerned, such as the permeability of the placenta to the K-radicle and the ability of the foetal liver to synthesize prothrombin, but in view of the consistent effect of prophylaxis by giving vitamin K to the mother before or during labour, they are probably relatively unimportant.

The results presented show that even immediate breast feeding, as is commonly employed in this hospital, does not diminish the extent of the fall in the prothrombin index. Cases in which diluted breast milk has been substituted for colostrum have given values of the prothrombin index almost identical to those of breast-fed babies (Macpherson *et al.*). That absorption of vitamin K can occur through the intestinal mucosa from the time of birth and can thereby prevent hypoprothrombinaemia is now established (Waddell and Guerry;[31] Macpherson *et al.*), and more recently Salomonsen[32] claimed that a similar result could be obtained by giving diluted boiled cow's milk to the infant during the first 4 days of life. He found that this treatment was more effective in summer than in winter, an observation clearly related to the raised K-content of cow's milk when fresh green feeding is available, and to similar seasonal variations in the diet of the mother. It appears from these observations firstly, that in the normal infant there is no defect in the mechanism of fat absorption which could contribute to the rapid fall in the prothrombin index; and secondly, that, in hospital patients at any rate, colostrum and breast milk contain less or less easily absorbed vitamin K than cow's milk. When, however, the mother's diet in pregnancy has been satisfactory, sufficient reserve of vitamin K may be stored in the foetus to maintain the prothrombin at normal or nearly normal levels beyond the period usually regarded as neonatal, even when the diet is absolutely K-deficient. It follows, therefore, that the extent of the initial fall in the prothrombin index is primarily dependent upon the vitamin K content of the mother's diet and upon the absorption of the vitamin from her alimentary canal, and that when these have been suspect, it may be increased by secondary factors such as complicated labour, or prolonged by temporary deficiency in the diet of the new-born infant. As the usual onset of persistent haemorrhage is within the first 4 days of life, during

the period when the prothrombin index remains at a low level after its initial fall, it is clear that dietary deficiency during pregnancy is a factor of great importance in the aetiology of haemorrhagic disease in the new-born. As a corollary, provided that the antenatal intake of "protective" foods is maintained at a high level (and herein, surely, lies one of the most important and most neglected aspects of antenatal care), and provided that there is no abnormality of fat absorption by the mother; or, when these conditions cannot be fulfilled, provided suitable vitamin K therapy be given to the expectant mother, haemorrhagic disease of the new-born should be preventable.

Summary

1. Various conditions of pregnancy and labour—pregnancy toxaemia, premature delivery, dietary deficiency of foods rich in vitamin K, prolonged labour—have been considered in relation to the degree and duration of hypoprothrombinaemia in the new-born.

2. Of these conditions, none had any constant effect upon the prothrombin index of the new-born except deficient diet during pregnancy. The children of mothers who gave a history of such dietary deficiency during pregnancy were found to show uniformly low values for the prothrombin index.

3. Prolonged labour *per se* did not adversely affect the prothrombin index in the new-born. By contrast, when prolonged labour was complicated by repeated interference under chloroform anaesthesia, the prothrombin index was found to be so low even at birth as to infer that prothrombin synthesis in the foetal liver had been depressed by the action of chloroform. The suggestion is made that chloroform may be toxic to the foetus *in utero* in a similar way and in the same circumstances as in the mother.

4. The evidence obtained from feeding 4 hydrocephalic babies on an absolutely K-deficient diet from the time of birth indicates that conditions of intake and absorption of vitamin K in the new-born do not affect the initial fall in the prothrombin index, but do influence the subsequent recovery towards normal. It appears, moreover, that in the absence of a dietary source, vitamin K cannot be synthesized by the intestinal flora and absorbed by the intestinal mucosa in sufficient quantities to maintain the level of the prothrombin index.

5. Fifteen cases of haemorrhagic disease of the new-born are reported in detail.

6. In 2 of these cases bleeding occurred as a complication of erythroblastosis foetalis (icterus gravis).

7. In every case of simple haemorrhagic disease in which the antenatal diet was investigated, there had been a grossly deficient intake by the mother of foods with a high vitamin K content. The incidence of other features of pregnancy and labour was quite irregular.

8. The most frequent site of bleeding was gastro-intestinal. A possible relation of this to the hyperacidity of the fasting-juice in the new-born is suggested.

9. Cerebral haemorrhage was proved to have occurred in 4 of the 15 cases of haemorrhagic disease. Two of these cases were in very premature babies. In every case, symptoms indicated that the effect of birth trauma had been accentuated by the hypoprothrombinaemia.

10. The belief is expressed that it should be possible to prevent haemorrhagic disease of the new-born by proper supervision of the mother's diet during pregnancy. When this has not been feasible, the same end can be achieved by adequate administration of vitamin K to the mother late in pregnancy or during labour.

Serial estimations in several of the cases reported have been made by Dr. E. McCallum, to whom I am very much indebted for her assistance throughout the course of this investigation. My thanks are also due to Dr. J. L. Henderson for much helpful criticism; to Dr. W. F. T. Haultain, Dr. Douglas Miller, Professor R. W. Johnstone and Professor Charles MacNeil for allowing me every facility to carry out this study on the cases under their charge; and to the Ward Sisters for their care and attention to matters of diet and administration of vitamin K-analogues. The vitamin K-analogues have very generously been supplied by Glaxo Laboratories Limited and by Roche Products Limited.

TABLE I.

		Hours After Delivery.							
Number		<24	<48	<72	<96	<120	<144	<168	<192
1	6345	98		75·5	61	60	74	82	80
	6344	94		80	63	64	73	78·5	76
2	5568	60	56·4	38·5	45·6	—	—	—	—
	5569	61·3	59·5	38	47·3	—	—	—	—

TABLE II.

Grade	I	II	III
Blood-pressure	>130/80	>150/90	>180/100
Albuminuria	>0.5 grams per litre	>2 grams per litre	>4 grams per litre
Oedema	Pressure pitting on tibia	Gross in extremities Present in face	Generalized
Eye signs	———	Muscae	Papilloedema Changes in retinal vessels Blindness
Other symptoms	———	Headaches, mild Insomnia	Headaches, marked Jaundice Vomiting Epigastric pain Oliguria

TABLE III.

		Cerebral symptoms	Haemorrhagic disease	Maternal P.I.	Hours After Delivery.										
					<12	<24	<48	<72	<96	<120	<144	<168	<192	<216	<240
cases	(37)	5	4	89.5	61.3	62.25	50.8	51.1	53.4	59.7	58.6	64.7	69.2	76.3	74.0
ormal elivery	(18)	3	1	90.5	55.8	65.5	49.0	55.0	55.8	59.2	60.9	66.6	67.75	72.7	—
de I	(7)	3	—	100.0	—	53.5	50.2	50.25	54.8	73.2	71				
de II	(16)	—	3	85.0	55.2	61.5	44.4	45.0	51.0	55.5	61.0	64.8	70.4	75.1	
de III	(9)	1	1	85.0	63.3	67.8	57.3	57.3	55.9	60.5	55.6	62.1	69.1	69.0	—
mpsia	(2)	1	—	106.0	73.0 91.0	— —	69.2 65.7	56.0 62.5	45.0 —	50.0	45.3	52.0	65.0	85.0	—
ration															
<5 weeks	(23)	5	3	87.5	62.3	62.4	52.3	55.7	51.7	61.1	60.8	68.9	72.5	75	
>5 weeks	(14)	—	1	93.5	59.8	61.9	48.8	43.7	55.3	57.8	55.7	60.8	62.8	76.5	

TABLE IV.

Type of delivery	Number	Haemorrhagic disease	Cerebral Symptoms	
			With low prothrombin index	With "normal" prothrombin index
Spontaneous	15	2	—	1
Caesarean section	4	1	—	—
Assisted delivery	18	1	3	1

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TABLE V.

		Mother			Labour			
No.	Serial No.	Antenatal condition	Diet	Proth. index	Duration	Type	Delivery	Birth-weight
1.	5551	Hypertension Grade 2	Deficient	75	—	—	C.C.S.	9¼ pounds
2.	5572	Apparently healthy	——	—	—	—	Spon. V.	6½ pounds
3.	5754	P.E.T. Grade 3 (6 weeks duration)	Deficient	95.5	10 hours	Easy	Spon. V.	4¼ pounds
4.	7233 (S.C.)	——	——	—	—	"Quick"	Spon. V.	n.k.
5.	6295	Hypertension Grade 2	Deficient	—	16 hours	Normal	l.f.d.	8 pounds
6.	6446	Healthy	Borderline	97	5 hours	"Quick"	Spon. V.	5½ pounds
7.	6531	Sickness and anorexia	Deficient	98	21 hours	Normal	Spon. V.	6½ pounds
8.	6633	Obese. Chronic cholecystitis	Deficient	—	115 hours	Inert	m.c.f.	n.k.
9.	6765	Hypertension Grade 2 Anaemic	Deficient	—	11 hours	Normal	Spon. V.	5½ pounds
10.	6780	——	Deficient	97	60 hours	Inert	Spon. V.	5¾ pounds
11.	6912	Indigestion	Deficient	91	—	Induced for A.P.H.	Spon. V.	2¼ pounds
12.	6913						Breech	2¾ pounds
13.	6947	Healthy	Deficient	87	36 hours	Normal	Breech	6½ pounds
14.	7152	Hypertension Grade 3	Adequate	83	6 hours	Easy	Spon. V.	5½ pounds
15.	7252	Healthy	Deficient	82	76½ hours	Trying	m.c.f.	8¼ pounds

Proth. index = Prothrombin index.
C.C.S. = Classical Caesarean section.
l.f.d. = Low forceps delivery.
m.c.f. = Mid-cavity forceps delivery.
n.k.
P.E

LE V.

BABY					REMARKS
weight	Complications	Type of bleeding	Time of onset	Proth. index	
ounds	Cut on shoulder	Superficial	28 hours	18.2	
ounds	Oesophageal atresia Operation; death	Post-operative into peritoneal cavity and gut	172 hours	32	Prothrombin index taken 2 hours before operation
ounds	Jaundice Abnormal fat absorption Anaemia	Superficial	161 hours	26.6	
	——	Alimentary Subcutaneous	84 hours	38	Prothrombin index taken 20 hours after onset
nds	——	Alimentary	40 hours	35	
ounds	Erythroblastosis Cerebral; death	Subcutaneous Submucous	Birth	34.5	Cord wound tightly round neck. P.M. Intracranial haemorrhage
ounds	——	Alimentary	32 hours	28	
	Pronounced cerebral symptoms	Superficial	60 hours	24	Three anaesthetics during labour
ounds	Anaemia	Alimentary	50 hours	37.6	
ounds	——	Alimentary	24 hours	35	
ounds	Cerebral Death 74 hours	Superficial Intracranial	24 hours	33	P.M. Bleeding into brain, liver, adrenals.
ounds	Cerebral Death 43 hours	Alimentary Intracranial	24 hours	30	P.M. Bleeding into brain.
ounds	——	Superficial Alimentary	90 hours	25	
ounds	Erythroblastosis	Superficial	184 hours	29	
ounds	——	Superficial Alimentary	30-40 hours	26.7	Three anaesthetics during labour. Manual rotation followed by forceps

n.k. = Not known.
P.E.T. = Pre-eclamptic toxaemia
Spon. V. = Spontaneous vertex delivery.
P.M. = Post-mortem examination.

The Importance of Increased Production and Excretion of Gonadotropic Hormone for Diagnosis of Hydatidiform Mole

BY

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THE importance of the increased excretion of gonadotropic hormone (prolan) for the diagnosis of chorionepithelioma was reported in another place.[1] That the demonstration of an increased excretion of gonadotropic substance in the urine is important for the early diagnosis of chorionepithelioma is now unanimously acknowledged in the literature.

In the observations made during the last few years, and reported in the following, we have renewed our inquiries on how far can the presence of a hydatid mole during pregnancy be diagnosed by hormone analysis. In a lecture to the Viennese Biological Society on April 15, 1929, I reported[2] that the excretion of gonadotropic substance in the urine in cases of hydatidiform mole is from two to three times as great as in normal pregnancy and that the concentration of this principle in the fluid of the mole is greater than in its walls. It was thus demonstrated that the production of gonadotropic substance in hydatidiform mole is greater than in normal pregnancy. Aschheim[3] has previously ascribed the formation of luteal cysts in the ovary in cases of hydatidiform mole and chorionepithelioma to a secretion of the anterior pituitary. The question remained as to whether in hydatidiform mole and in pregnancy more hormone is actually produced or whether more is just retained.

The demonstration of the highly increased production of prolan, e.g. the possibility of bringing about the hormonal pregnancy reaction with strongly diluted urine as well as with spinal fluid, is the safest sign for the diagnosis of chorionepithelioma as well as the earliest sign for the presence of metastases. The diagnosis of a hydatidiform mole is not at all easy. It is most important to assure this diagnosis because of the danger of des-

troying a normal pregnancy. When the suspicion of a hydatidiform mole exists, we should, therefore, never rely on a single examination, but base our diagnosis on several hormone analyses. Especially important is the increment in the hormone titer in urine, blood and spinal fluid. In a patient whose uterus was larger than what should have corresponded to a third month of pregnancy, I first found on urine titration[4] 50,000 MU prolan B per liter morning urine, and on a further examination a rapid increase to 200,000 MU. This abnormally steep increase of the hormone titer pointed to a hydatidiform mole, which was later confirmed also clinically. The diagnosis of hydatidiform mole from the urine is possible only when at least 200,000 MU per liter prolan B are found on repeated examinations and when an increase in the hormone titer takes place[4].

Does the strong increase in prolan excretion during the first months of pregnancy point with certainty to the presence of a hydatidiform mole? In early pregnancy the content of this substance amounts to an average of 10,000 mouse units per liter of blood and from 5,000 to 30,000 mouse units per liter of morning urine[5]. Production of gonadotropic principle may be increased in gestation toxicosis (G. van Smith and O. W. Smith[6]) in such a fashion that amounts near those obtained in hydatidiform mole may be discharged in the urine. The increased excretion, therefore, indicates the presence of a hydatidiform mole only if toxaemia of pregnancy can be excluded. The question of toxaemia is hardly important in relation to the prolan titer in the early months of pregnancy, because the production of prolan is generally unchanged in vomitus gravidarum. Of importance is the fact, however, that a sudden increase in prolan excretion takes place 2 months after fecundation. The results of Browne and Venning[7] show that there is a maximal concentration of gonadotropic substances in the urine (100,000-300,000 rat units per liter) between the 50th and 60th day after the beginning of the last menstrual period, the rise to this maximum occurring sharply between the 40th and 50th day. The peak lasts only a very short time, sometimes only a few days, and is followed by a rapid fall in concentration between the 65th and 85th day, to 20,000-40,000 RU. Thereafter, the decline is more gradual, reaching a level of 3,000 RU by the 120th day. F. Laquer, Döttl and Friedrich[8] have performed systematic examinations of the prolan content of urine during the various months of pregnancy. They found the highest value (300,000 RU per liter) in the 6th week of pregnancy, while on the 9th week it amounted

to 100,000 RU and in the 13th to 50,000 RU. Evans, Kohls and Wonder[9] found a high hormone peak at a time which is quite accurately one month from the beginning of the first expected but missed menstruation. In 6 cases the maximal values varied between 75,000 and 750,000 RU, in one case the daily hormone output amounted to 1,040,000 RU.

Thus, from the end of the 1st to the end of the 2nd month of pregnancy a sudden, short-lasting increase in hormone content of the urine takes place, so that during this period the diagnosis of hydatidiform mole may be erroneously made. The maximal concentration of prolan in the urine during the peak is, according to Browne and Venning, 40,000 RU per liter, and according to Laquer c.s. 300,000 RU. Special attention must be called to the fact that the pregnancy reaction is not performed in the infantile rat but in the infantile mouse which is 3 to 5 times less sensitive than the rat.[10] On changing the RU into MU we obtain peak prolan values of 8,000-60,000 MU per liter, as given by the various authors. These values are much smaller than those found in hydatidiform mole. Evans found higher values reaching 750,000 RU, and in one case even 1,040,000 RU or 208,000 MU. In this case one could assume a hydatidiform mole. Hence a confusion with hydatidiform mole may be avoided when more than one analysis is made, since this sudden overflow of hormone is of short duration. Furthermore—and which is most important—only when a continuous increase in the hormone titer is observed on repeated analysis can we make with certainty the diagnosis of hydatidiform mole.

Method of analysis. As is well known, the hormonal pregnancy test (AZT) is based on the demonstration of an increased excretion of gonadotropic hormone in the urine. These gonadotropic reactions are brought about by 2 different hormones, namely the anterior pituitary reaction (APR) I (follicle maturation) by prolan A and the APR II (follicle haematoma) and APR III (corpus luteum) by prolan B. A positive APR II or III are necessary for the diagnosis of pregnancy, the presence of APR I (oestrous-reaction) may only raise the suspicion of a possible pregnancy. The presence of prolan A is not sufficient for the diagnosis of pregnancy, because in certain forms of amenorrhoea and also in certain tumours it is excreted in increased quantities in the urine.[11] Nevertheless, the APR I is still of some importance for some problems in connexion with pregnancy. When the placenta has ceased to function, prolan B disappears from the urine much quicker than prolan A. Therefore, a posi-

tive prolan A reaction is sometimes found in cases of extrauterine pregnancy, which fact may serve as an important diagnostic aid. The exceedingly high production and excretion of prolan A in cases of malignant degeneration of the placenta may be of importance for the diagnosis and prognosis. I have reported in another place on the importance of this fact in chorionepithelioma.[1]

In the following it will be seen that the demonstration of an increased production of prolan A may be of importance also in the diagnosis of hydatidiform mole. The demonstration of prolan A is possible only when the pregnancy reaction is performed in infantile mice, because the A reaction (oestrous) will be easily seen in the vaginal smear. Rabbits are very sensitive to prolan (Zondek[10]), so that even 5 to 10 mouse units are sufficient to bring about the gonadotropic reaction, although an infantile rabbit is 120 times heavier than an infantile mouse. On the basis of these observations Freidman has modified the original AZT by injecting the urine intravenously in rabbits instead of subcutaneously in mice. The diagnosis of pregnancy, as in the AZT, is based on the presence of follicle haematoma. The demonstration of the APR I is not reliable in rabbits. Since the demonstration of prolan A, as previously carried out, makes possible certain diagnostic conclusions, I think that the original method should be used for the diagnosis of hydatidiform mole or chorionepithelioma, e.g. the urine should be examined in infantile mice.*

To demonstrate an increased excretion of gonadotropic hormone, the highly diluted urine should be injected in infantile mice. Since the existence of a hydatidiform mole may be assumed only when at least 200,000 MU prolan B per liter urine are present, 0.005 c.c. must be sufficient to bring about a positive reaction. To make this possible, 1 c.c. urine, for example, is diluted with 99 c.c. water, and in the course of 48 hours 4 times 0.1 c.c. and twice 0.05 c.c. are injected subcutaneously. Spinal fluid is injected either native or diluted. In normal pregnancy prolan A may sometimes be found in the spinal fluid, but never prolan B. The latter will be found in the spinal fluid in hyda-

* We found that the use of rabbits in the subtropical climate of Palestine is not suitable for the quantitative determination of prolan, and thus also not for the pregnancy test, because follicle haematoma may come about spontaneously by climatic changes and especially in spring and autumn by the shirocco (dry east wind). Sometimes we noticed also a decreased sensitivity towards prolan in the winter.

tidiform mole and chorionepithelioma, when the body is overflown with prolan. The demonstration of prolan in the spinal fluid is, therefore, diagnostically of special importance.

Prolan is found in colostrum during a normal pregnancy only from the 7th month and on, in hydatidiform mole in the 4th month already.[12]

I was not able to demonstrate the presence of prolan in saliva, neither in a normal pregnancy nor in hydatidiform mole or chorionepithelioma.[13]

The fluid of the mole is rich in prolan. This fact, as mentioned above,[2] drew our attention to the increased production of gonadotropic hormone in hydatidiform mole. In the examination of hydatid tissue[14] and uterine mucosa the following method was used:

The tissue is weighed and then covered with 100 c.c. of acetone. A few days later the acetone is twice replaced till a water-free dry acetone-powder is obtained; this is finely ground. The powder is then extracted for several hours in a shaker with (*a*) distilled water, (*b*) n/100 NaOH and (*c*) n/100 HCl. The three extracts are mixed, if necessary neutralized, then filtered and their prolan contents analysed in infantile mice.

Hormone analysis in three different forms of hydatidiform mole are reported in the following.

I. Mola Destruens

M. C., 40 years old, 6 deliveries, 1 abortion. The patient was admitted to our department in May, 1940, because of haemorrhage in the 4th month of pregnancy and a very bad, febrile general condition. The case was considered an infectious abortion and treated by the conservative method (chinin and pituitrin). Placental tissues were expelled, and on macroscopic examination already partial hydatidiform mole formations were identified; this was confirmed on anatomical examination. The hormone analysis gave the following results:

1. Urine: 50,000 MU prolan A and B per liter urine.
2. Spinal fluid: 2,000 MU prolan A and B per liter.
3. Saliva: less than 333 MU prolan A and B per liter.

In the course of the following days a general septic condition developed with chills and intermittent fever. The patient received a continuous intravenous glucose-alcohol drip infusion for several days. We have been using this method[15] with good results in the treatment of septic puerperal infections. Also in

this case the treatment was successful; the patient's general state of health greatly improved, and a curettage was performed one month later. On introduction of a curette the uterine tissue, which was found to be extremely friable, was perforated, so that a vaginal extirpation of the uterus was immediately performed. In the dissected uterus only a few hydatids were observed. Above the cervix—where the curette penetrated the uterine tissue—infiltrative growth in the uterine muscle could be seen macroscopically. The histological examination (Prof. E. E. Franco) confirmed that the mole formation had penetrated deeply into the muscle reaching the serosa; penetration into the blood vessels was not observed.

Four weeks after operation the prolan contents of the urine had fallen to 333 MU per liter (50,000 MU on previous analysis). The urine was controlled at intervals of 2 months. The pregnancy reaction always remained negative, which meant that a metastatic chorionepithelioma could be excluded.

In the case under examination we are dealing with a destructive mole which was responsible for the perforation with the curette. This case shows that a destructive mole does not differ hormonally from a typical hydatidiform mole. The value 50,000 MU prolan B is not at all high; on the contrary, the diagnosis of a hydatidiform mole cannot be based on such a value. It has been said above that a positive pregnancy reaction brought about with 0.02 c.c. morning urine, i.e. the demonstration of 50,000 MU prolan B per liter, suggests only the suspicion of a pathological change in the placenta. Only on demonstration of at least 200,000 MU prolan B per liter urine, after exclusion of toxaemia, can the diagnosis of hydatidiform mole be made. Furthermore, this value has to be obtained on repeated analysis with the titer progressively increasing. In the present case we have carried out the hormone examination only after the mole has been partially expelled, which means that the connexions with the maternal circulation have been partially interrupted. Had any analysis been made at an earlier date higher hormone values would have most probably been obtained. Nevertheless, these could not have been very much higher because a certain amount of hydatid mole tissues was still present in the uterine muscle. Had the villi undergone malignant degeneration (chorionepithelioma) these would have been sufficient to effect an excretion of several hundred thousand mouse units of prolan B per liter urine. The fact that the infiltrative growth of the hydatidiform mole caused only a relatively small production and ex-

cretion of prolan indicates that this infiltrative growth did not assume a malignant character. It is well known that moles may burrow into the blood vessels, reach the parametrium and even give forth metastases without assuming a malignant character. Robert Meyer[16] found that most intravenous hydatidiform moles are not associated with malignant epithelial growth and that hardly 10 per cent of them are malignant. In 5 cases of hydatidiform mole, Meyer found a more or less deep penetration of villi. The fact that the destructive mole is mostly not malignant will account for the not exceedingly high hormone titer. The relatively low titer found in our case shows that anatomically the process was certainly not malignant.

II. Hydatidiform Mole and Luteal Cysts

R. E., 18 years old, married 8 months. Last menstruation in September, 1937. The patient was admitted to hospital on Jan. 21, 1938, with severe haemorrhage. The placenta which for the most part consisted of hydatid moles was spontaneously expelled. Because of the strong haemorrhage which ensued, a curettage had to be performed. One week after curettage (Jan. 29, 1938) two mobile tumours were found on examination, on both sides of the uterus. The right tumour was of the size of an apple, the left that of a grape fruit. The diagnosis of luteal cysts associated with hydatid mole was made.

On general examination nothing of interest was found. Blood and urine were normal.

Hormone analysis. The morning urine contained at least 50,000 MU prolan A and B per liter.

The patient left the hospital on Feb. 2, 1938, with the intention of returning for further examination. She was readmitted to hospital 2 weeks later because of severe uterine bleeding. On examination the uterus was found enlarged and very soft, the right tumour was of the size of a mandarine and the left tumour of the size of an orange, i.e. the tumours had thus diminished in size.

Examination on Feb. 17, 1938: In the morning urine less than 50,000 MU prolan A and B per liter were found, a regression, therefore, in prolan excretion. Further analysis performed regularly at intervals of 2 weeks showed that the prolan excretion decreased considerably, but prolan was still present in quantities sufficient to bring about a positive pregnancy reaction, i.e. at least 400 MU prolan B. We found:

on March 29th, 1938, 51 days after curettage, 1000 MU prolan B,
on April 26th, 1938, 78 days after curettage, 2500 MU prolan B,
on May 10th, 1938, 92 days after curettage, 1000 MU prolan B.

In normal pregnancy the excretion of prolan B ceases a short time after expulsion of the placenta, in general the pregnancy reaction is negative after 7 days. In hydatidiform mole prolan excretion may be prolonged, generally lasting 4 weeks; in rare cases the AZT will still be positive after 3 months. In a case of hydatidiform mole Aschheim found a positive APR I after 6 weeks, and in another case a positive APR I, II and III after 10 weeks.

Since in our case a positive pregnancy reaction was still present 92 days after curettage, it was clinically most important to decide whether a chorionepithelioma or a luteal cyst was responsible for the increased excretion of prolan. Were this a case of chorionepithelioma the uterus of this 18-year-old woman would have to be extirpated; if the positive pregnancy reaction was caused by a luteal cyst, this mutilating operation could be avoided. In this case we performed a curettage and puncture of the right cyst with aspiration of its contents through the pouch of Douglas. (May 12, 1938.) I have used this method for many years and with good results in cases of follicle cysts, i.e. polyhormonal disturbances.[17] Urine, blood, colostrum and saliva analysis were performed before curettage. The following results were obtained:

Material	Prolan A MU per liter	Prolan B MU per liter
Urine	2500	1000
Serum	10,000	2500
Colostrum*	<555	<555
Saliva	<333	<333

In general, during pregnancy the hormone titer in the blood is lower than in the urine, because the body endeavours to eliminate the hormone as soon as possible. In hydatidiform mole we often find, as will be seen also in our next case, a higher hormone concentration in the blood than in the urine. In the present case we find in the blood 4 times as much prolan A and 2.5 times as much prolan B as in the urine. On aspiration, 30 c.c. of a clear yellowish serous-like fluid were removed from the ovarian cyst

* Both breasts were still rich with colostrum 3 months after expulsion of the hydatids.

(luteal cyst). This fluid contained 5500 MU prolan A, 550 MU prolan B and 2000 MU oestrogenic hormone per liter. It was thus determined for the first time, so far as I can gather from the literature, that luteal cysts contain a fluid rich in hormones. Of special interest seems to me the fact that after aspiration of the cyst content the prolan excretion has immediately decreased, and soon ceased. While 92 days after expulsion of the mole the pregnancy reaction with urine was still positive (which means more than 400 MU prolan B per liter) one week after the puncture of the cyst, the AZT was negative and remained so. The objection may be made, that the curettage of the uterine mucous membrane has removed the remainder of the hydatids, and this was responsible for the passage from a positive to a negative reaction. This is certainly not the case since (1) macroscopically and microscopically, moles were not to be demonstrated, and (2) the hormone analysis of a part of the material obtained on curettage gave the value of <43 MU prolan per gramme of fresh tissue, which speaks against the presence of hormonally active tissues. It is difficult to explain why the pregnancy reaction should become negative after puncture and aspiration of the luteal cyst. Since uterine hormonally active tissue was not present, the only possibility left is that the gonadotropic hormone is produced in the luteal cysts or in the hypophysis. According to general agreement the hyperproduction of prolan during pregnancy is of placental and not hypophysarean origin. Judging from all evidence presented in literature for the correctness of this assumption, I find that it has not yet been decisively proved. However, if we accept this as a fact, we have to conclude that in our case only the luteal cysts may be considered the hormone-producing source. This possibility will explain why, after the aspiration of the contents of the cyst, the pregnancy reaction, which has been positive for 92 days, has suddenly become negative.

III. Transformation of Hydatidiform Mole into Chorionepithelioma

M. C., 22 years old. One delivery and one abortion prior to admission to hospital. Following treatment in some other hospital the patient was admitted on Nov. 4, 1940, to our department because of haemorrhage during pregnancy, deteriorated general condition and septic fever. Two months earlier the patient had a curettage for an incomplete abortion. It seems that at that

time already, a hydatidiform mole was removed. On admission, we found the uterus larger than the presumed pregnancy. The patient was very anaemic and had septic intermittent fever, and hydatidiform villi were spontaneously expelled through the vagina. A few days after admission we performed hormone analysis. We were unable to treat the hydatidiform mole, because the patient's condition had rapidly deteriorated and she suddenly died, a few days later, of pulmonary oedema.

Hormone analysis. The examination of the urine, blood, saliva and spinal fluid gave the following values:

Urine	at least	500,000	MU prolan A/ liter
		250,000	MU ,, B/ ,,
Serum		3,000,000	MU ,, A/ ,,
		300,000	MU ,, B/ ,,
			less than 333 MU oestrin/liter.
Saliva		333	MU prolan A/ liter
	less than	333	MU ,, B/ ,,
Spinal fluid		1666	MU ,, A/ ,,
		600	MU ,, B/ ,,

The prolan values in the urine were those common in hydatidiform mole (250,000 MU B/liter). Prolan A values were twice as high as prolan B, which is often found in pregnancy and in hydatidiform mole. In the saliva, prolan A was detected, while prolan B was not. A positive pregnancy reaction was obtained with the spinal fluid, which is an important sign of hydatidiform mole. While the prolan values in the blood during pregnancy are much higher than in the urine, in this case—as well as in case II—the opposite is true. Prolan B in the blood amounted to 300,000 MU per liter while in the urine to only 250,000 MU. Especially striking is the high content of prolan A in the blood; it amounts to 3,000,000 MU per liter, which is 6 times higher than that in the urine. I met such high values of prolan A in blood only in chorionepithelioma.[1] The prolan A content in itself cannot be utilized for the diagnosis of a normal or pathological pregnancy; nevertheless, it may serve as an important diagnostic aid. An exceedingly high A content during pregnancy suggests the suspicion of a hydatidiform mole; while in the case of an existing mole, it suggests a chorionepithelioma.

On the basis of the blood analysis, I concluded that in this case a transformation of a hydatid mole into chorionepithelioma must have taken place. The macroscopic appearance of the uterus, which was removed on post-mortem, was, contrary to the above view, typical of hydatidiform mole. The hormone

analysis of the hydatid mole itself also spoke against the assumption of a malignant degeneration: the fluid of the mole contained 400,000 MU prolan A and 250,000 MU prolan B per liter. These values correspond to those I found in other cases of hydatidiform mole; at any rate our experience in this direction is still limited. After expression of the hydatid fluid, the chorionic tissue was analysed according to the method described above. We thus found that 7 mgm. of fresh tissue contained 1 MU prolan A and that 21 mgm. of fresh tissue contained 1 MU of prolan B. These values when compared with those I previously obtained in analysis of hydatid tissue[1] should be considered low. At the time, I found that in 4 to 6 mgm. of fresh tissue, already, 1 MU prolan A and B could be found. The macroscopical appearance, as well as the above-mentioned hormone analysis of urine and tissue, negative a malignant degeneration of the mole, while the exceedingly high values in the blood lead to the conclusion of chorionepithelioma. Since this case appeared to me of primary importance I asked our pathologist, Prof. E. E. Franco, to examine the uterus most carefully. On examination of 10 different parts of the uterus malignant degeneration was not found. I therefore asked for further sections of the remaining part of the uterus. In the 12th piece examined a doubtless malignant degeneration was found at one point, so that on the basis of this finding we were able to make the final diagnosis of "chorionepithelioma." Had not the hormone analysis encouraged this extensive anatomical examination, this case, most probably, would not have been recognized as chorionepithelioma. Had the hormone analysis been made at the beginning of the illness and the diagnosis of chorionepithelioma made at that time, an immediate operation might have saved the life of this young woman. This case, I think, shows most strikingly how important are the hormone analyses for the early diagnosis of chorionepithelioma. As has been seen in this case, we should not be satisfied with the urine analysis alone, but serum and spinal fluid analyses should also be made.

Discussion and Conclusions

We have reported above on the hormone analyses in three special cases of hydatidiform mole and have demonstrated the importance of the increased production and excretion of gonadotropic hormone for the diagnosis of hydatidiform mole.

1. *Diagnostical importance of increased excretion of prolan A.*

While the diagnosis of pregnancy is based on the increased production of luteinizing hormone (prolan B) alone, the presence of prolan A is important for the diagnosis of hydatidiform mole, provided that the production of prolan A takes place in exceedingly high quantities. It is difficult to give any fixed values, but, in general, we may say that should the titrated values rise to at least 500,000 MU prolan A and 200,000 MU prolan B per liter urine we have to assume with the greatest probability the presence of a hydatidiform mole.*

2. *Occurrence of high prolan A and B titer in the blood.* While during pregnancy the body is inclined to eliminate with the urine the hormone present in the blood—the hormone titer of the serum thus being lower than that of the urine—the contrary might be the case in hydatidiform mole. In a case of hydatidiform mole with luteal cyst (case II) the prolan A values of the serum amounted to 10,000 MU and those of the urine to only 2500 MU per liter; the hormone concentration in the blood was, therefore, four times higher than in the urine. Also the prolan B value was higher in serum than in urine, 2500 MU as compared with 1000 MU per liter. In case III we had to deal with a transformation of a hydatidiform mole into chorionepithelioma, in which the malignant degeneration was anatomically demonstrated in only one spot. The diagnosis was based on the exceedingly high value of prolan A in the serum (3,000,000 MU per liter). The prolan A value in the blood is 6 times as high as that in the urine.

These two cases demonstrate that we should not be satisfied with the urine analysis alone for the diagnosis of hydatidiform mole, and that the hormone analysis of the serum for prolan A and B is indispensable. Since the demonstration of prolan A is unobjectionable only in infantile mice and is not possible in rabbits, the performance of the reaction with infantile mice is recommended, i.e. the original method of Aschheim-Zondek and not the modification according to Friedman.

3. *Determination of prolan in the spinal fluid.* In normal pregnancy prolan is not to be found in the spinal fluid, sometimes prolan A, however, but never prolan B. In cases of excessive production of prolan, taking place only on degeneration

* It should not be overlooked that very few cases of hydatidiform mole have been described in literature which lacked increased excretion of prolan. This shows that the negative prolan findings does not exclude absolutely the possibility of a mole.

of the placenta, the blood-liquor barrier is overcome and prolan B is to be found in the spinal fluid. Should it become possible to obtain a positive pregnancy reaction (APR II or III) with the native spinal fluid, i.e. to demonstrate 400 MU prolan B per liter, it would point to a hydatidiform mole, respectively chorionepithelioma. The higher the prolan B values in the spinal fluid the more certain is the diagnosis. In the above-mentioned cases we found in mola destruens 2,000 MU prolan A and B per liter, and in the beginning of a chorionepithelioma (case III) 1,666 MU prolan A and 600 MU prolan B per liter.

4. *Prolan determination in other fluids.* The demonstration of the hormone in the saliva or colostrum has no diagnostic significance. We, therefore, need for the diagnosis of a malignant degeneration of the placenta analysis of (*a*) the serum, (*b*) urine and (*c*) cerebro-spinal fluid.

5. *Determination of prolan in the tissue.* The demonstration of gonadotropic hormone in tissues is also of diagnostic importance. Since the placenta is rich in gonadotropic hormone, the demonstration of at least 800 MU prolan B per gramme of fresh tissue obtained by curettage will be necessary to assure the diagnosis of malignant degeneration. When we find in an extragenital tumour 100 MU per gramme of fresh tissue this will indicate a metastatic or extragenital chorionepithelioma (hormone-tissue diagnosis). The method of hormone extraction is described above.

6. *Different forms of the hydatidiform mole.* (*a*) Mola destruens. The mola destruens does not differ in its hormone production from an ordinary hydatidiform mole. We cannot conclude malignancy from infiltrative growth alone, not even in those cases in which the moles penetrate the blood vessels and give metastases. The intravenous hydatidiform mole may progress without malignant degeneration. In these cases the prolan values are of particular importance. As long as the prolan A and B values in blood and urine are below 200,000 MU per liter there is no fear of a malignant degeneration. Higher values point to a malignant degeneration. In these cases an exceedingly high production of prolan A is also of diagnostic importance. Hormone titer of over 500,000 MU prolan A per liter in the blood or urine speak for a malignant degeneration, values of several millions point conclusively to such a degeneration. Only in such cases can the hormonal analysis be decisive for the diagnosis.

(*b*) Luteal cyst in hydatidiform mole. While in the normal pregnancy the prolan excretion ceases one week after the separa-

tion of the placenta, in hydatidiform mole this is usually more prolonged, it may last 4 weeks and in some cases even 3 months. When hydatidiform mole is accompanied by luteal cyst the duration of excretion is almost always prolonged. In the case described above the pregnancy reaction with urine was still positive after 92 days. As soon as the fluid in the luteal cyst was aspirated the hormone excretion immediately ceased and the pregnancy reaction became negative and remained so. Why the puncture and aspiration of the luteal cyst should stop the hormone excretion is yet hard to say with certainty. Of interest is the fact that the fluid of the cyst was rich in gonadotropic hormone. It contained 5,500 MU prolan A and 550 MU prolan B per liter. It is possible that in a luteal cyst the gonadotropic hormone is produced in the ovary.

(*c*) Transformation into chorionepithelioma. Case III clearly demonstrates the importance of the hormone analysis in hydatidiform mole. This seemed to be an ordinary case of hydatidiform mole except that the exceedingly high value of prolan A in the serum (3,000,000 MU per liter) pointed to a malignant degeneration. On the basis of this analysis the uterus was anatomically thoroughly examined until we succeeded in demonstrating the malignant degeneration at one point. Had not the hormone analysis pointed otherwise, this case would have been considered an ordinary hydatidiform mole. The earlier were the diagnosis of chorionepithelioma made, the greater would have been the hope of saving the life of this young woman. The earlier diagnosis is possible only with the aid of the hormone analysis, and herein consists also its main value.

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The Dystocia Dystrophia Syndrome*

BY

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THE name dystocia dystrophia syndrome has been given by De Lee[1] to an obstetrical condition that is of great clinical importance and aetiological interest. In the 1938 edition of his *Principles and Practice of Obstetrics* he describes the following features of the condition: (1) Slightly justo-minor or masculine type pelvis, with girdle obesity and other signs of dystrophia adiposogenitalis (hypopituitarism), small cervix, narrow rigid vagina; (2) aged primiparity; (3) overmaturity of the child (prolonged pregnancy); (4) non-engagement of the foetal head when labour begins; (5) occipito posterior position; (6) premature rupture of the membranes; (7) weak pains with protracted 1st stage of labour; (8) familial dystocia; (9) tendency to eclampsia.

Horner[2] (1927), according to De Lee, drew attention to this syndrome. In reviewing a series of cases of prolonged labour, he describes the features of this condition. The patients are short in stature. There is a male distribution of hair, and the bones of the pelvis are thick and heavy and with a narrow pubic arch. The forearms and fingers are short. The vagina is tight and shallow, and the pelvic floor is rigid. Pregnancy may not occur for many years. There is a tendency to abortions and toxaemia. Pregnancy frequently goes over term, and there is early rupture of the membranes. The babies are relatively large, and the head fails to engage. A short labour without risk to mother and baby is rare.

A few other references, mainly in American literature, have been made to this syndrome, or to related ones, under varying names. Thus Welz[3] speaks of a pregnancy in a case of "improved sporadic cretinism." His patient was 36 years of age, obese, with short forearms, and had been married for 14 years without a previous pregnancy occurring. Menstruation had been

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irregular, and the pelvis had male features. Caesarean section was carried out, and milk secretion was absent during the puerperium. Greenhill[4] uses the term "dystocia dystrophia syndrome." He refers to the relative sterility in these patients. There is frequently only one pregnancy, and the patients conceive late. In their nature they are heavy set, with short extremities, and have masculine and hyperpituitary characteristics. The available pelvic space is small. There may be a family history of dystocia. The patients go beyond term, there is early rupture of the membranes with weak irregular pains, and the position is an occipito posterior one. Greenhill describes 7 cases, and strongly advises lower segment Caesarean section. Cornell[5] finds these patients to have a history of dysmenorrhoea or irregular menstruation, with relative sterility. They are prone to toxaemia, especially eclampsia, and all go over term 2 weeks or more. The babies are large and have hard bones. There is early rupture of the membranes, spontaneous delivery is rare, and the occiput lies posteriorly or transversely. He advises against induction. Daniels[6] refers to the condition under the name of "dystocia dyspituitarism," and emphasizes the importance of the pituitary factor. He quotes 3 cases of his own, and describes these patients to be short in stature with a short neck and broad hips. There is a history of dysmenorrhoea, amenorrhoea and abortions. The vagina is narrow, and vaginal examination is difficult. The bony outlet of the pelvis is thick, but its size is not reduced. He considers that they do not go over term. Labour is slow, and contractions are painful. Occipito posterior positions are usual, and spontaneous delivery rare. He also advises against induction of labour, and recommends Caesarean section. Goodall[7] describes the "inertia syndrome." The cases conform to a type, there may be male characteristics, and the disturbance is primarily an endocrine one. Inertia is a prominent feature. There is an abnormal rhythm of smooth muscle. He considers that the inertias of labour constitute in Canada the most common cause of difficult exhausting labour, with the highest percentage of maternal and foetal morbidity and death. McMann[8] describes the condition in some detail. It occurs in elderly primiparae, usually a long time after marriage. He considers that it is due to hypopituitarism. His description of the anatomy in these cases and of the type of pregnancy and labour, corresponds with those already quoted. He considers that prenatal care should foresee the type of labour, and that the condition is fairly easy to recognize, certainly once labour

has started. Caesarean section is the conservative way of terminating labour.

The syndrome has always seemed to me to be an important one, and though by no means rare, it is not generally recognized. I have thought it worth while, therefore, to report the history of 62 patients whom I have observed in the course of 8 years up to 1939, and of which the notes have been available. In some of these cases, unfortunately, the notes have proved to be deficient in what now appear to be important details, but on the whole they are adequate to form a picture of the main features of the condition.

Incidence. The clinical material has been collected from the practice of 5 maternity hospitals or units, and a very small number of them were attended in the district of one of these hospitals. The incidence is difficult to judge, as only the more striking cases are likely to attract attention. Daniels estimates it to be 3 to 5 per cent, but this seems to be too high, and I would place it among hospital cases as about 1 in 200 of all deliveries, or 1 in 80 primiparae. It is thus seen to be far from rare in the practice of the obstetrician.

Age. The average age in these 62 patients was 28. This compares with an average age of 25 in a series of 50 primiparae delivered at Walton Hospital. There were 7 patients of 35 or over, and 2 over 40. This evidence is not confined to older patients, however, as one patient was 19, and there were several round about 20.

General and gynaecological history. Details of the previous general and gynaecological history were not always available. Rheumatism was noted 4 times, fits and migraine once, rickets once, nephritis twice, scarlet fever twice, cardiac disease once, mastoid disease once, and in one case, a primigravida, there had been a breast abscess 9 years before.

There was a history of dysmenorrhoea in 4 cases, of irregular periods in 2 cases, of scanty periods in 2 cases, of dyspareunia in one case, and of a gynaecological operation in one case. Details of the time since marriage were available in 11 patients. In 3 this was less than one year, in one patient 1 to 2 years, in 4 patients 2 to 3 years, in 2 patients 3 years, and in the remaining patient 7 years without contraception having been practised. Considering that details about the previous history were somewhat deficient in most cases, it is thus seen that there is a rather high incidence of menstrual irregularity and of sterility. On the other hand, it must be pointed out that there were also many

cases in single girls or in patients who had been married after conception.

Previous and subsequent pregnancies. Only one patient had had a previous full-time pregnancy. That pregnancy seemed from the clinical history to have been similar to the pregnancy now being considered, and had ended in a Caesarean section. Four patients had had 5 miscarriages between them.

Eight patients are known to have had a subsequent pregnancy. The course of one of these is unknown. Three of them had a normal delivery. One was terminated again by a difficult forceps-delivery and a stillbirth. In another two normal delivery occurred, but a manual removal of an adherent placenta was necessary in both. In both of these there had been an intra-partum infection in the first pregnancy, in one case with gas-forming organisms. In the 8th case, a further pregnancy 2 years later was terminated by Caesarean section. During labour the pains were described as being weak and ineffective. An ear was presenting, and a baby weighing 8 pounds 10 ounces was delivered.

Many of the patients in this series were seen some years ago, and it is likely that a considerable number would have come under observation again had further pregnancy occurred. It seems that in these patients conception is difficult, or if conception does occur, that there is a considerable chance of one-child sterility following. Obviously there is very high relative value of the foetal life, and the bearing of this on treatment will be discussed later.

Only patients reaching term have been considered in this survey. It is probable that a careful analysis of cases of abortion would show many cases of this type.

General clinical features. In 6 patients there was found to be obesity worthy of mention, in one of these cases the patient being described as being both short and fat. In 5 a male distribution of hair on the abdomen was noted. Small fibroids were found on examination in 3. One patient was described as having greyish hair, and 2 others were described as being heavily built and of masculine type respectively. There was a high incidence of pelvic contraction and deformity. The examinations were made by many different observers, but the conditions found may be grouped into 15 cases of generally contracted pelvis, 10 cases of funnel pelvis, and one case of flat pelvis. Vaginal examination was found to be difficult or impossible in 13 patients for various reasons; usually because of resistance

to examination, but in some the vagina was narrow, or the introitus small or fibrous. Most of these points have been emphasized by De Lee.

Pregnancy. Toxaemia occurred in 36 cases, or in well over one-half of all the cases. In 7 others, a trace of albumin was noted sometime during pregnancy. In 31 of these cases, the toxaemia was of moderate or severe degree, as indicated by a high blood-pressure, the presence of oedema, and albuminuria with casts. Oedema was often a very striking feature, and in 3 cases increasing oedema during labour was noted. Oedema of the vulva was often prominent, and tended to cause difficulty in delivery, together with increased sepsis and poor healing of lacerations or episiotomies. Eclampsia occurred in 7 cases. In 5 of these, the fits commenced during the 1st or 2nd stages of labour, and in the 2 others, the exact time of onset was uncertain. Strong pains at the end of the 1st and during the 2nd stage in these cases in which disproportion and malposition are so common are probably responsible for precipitating eclamptic fits by raising the blood-pressure in patients already in the pre-clamptic state.

Time of onset of labour. There were 51 cases in which the dates were accurately known, and in which the expected date of delivery could be worked out by the usual approximate method. In one patient, labour commenced 8 days prematurely, and in 3 on the expected date of delivery. The remaining 47 commenced labour after the expected date of delivery, and the average time between this date and the date of delivery in these cases was found to be 17 days. In 13 cases this period was over 3 weeks, in 7 over 4 weeks, in 3 over 5 weeks, and in 2 over 6 weeks. Drug inductions were usually unsuccessful in bringing about the onset of labour, even when repeated. In one case, a stomach tube induction was carried out 6 weeks after the expected date of delivery with success. The tendency in these patients towards prolonged pregnancy and the difficulty in stimulating the uterus into action are thus obvious.

Labour and delivery. The average length of the 1st and 2nd stages of labour in 46 patients in which details were available amounted to over 50 hours, comparing with an average of 21 hours in a series of 50 primiparae in Walton Hospital. Moreover, in many cases there were slight pains for many days before the real 1st stage pains were considered to have begun. Pains tended to be weak through the 1st stage. In some cases they were hardly felt by the patient, but in others they were very

distressing although labour was not progressing, and they required repeated sedatives for their relief. There did not tend to be any sharp dividing line between the 1st and 2nd stages, and the down-bearing stage was seldom reached. The exact time of rupture of the membranes was not always recorded, but it is described as being premature, early or in the 1st stage in 20 patients. In not a single case in the whole series did a spontaneous delivery take place. The forceps was applied in 48 cases. In 11 of these patients the head of the child was more or less fully rotated. In 25 cases the head was in a position of transverse arrest. In 12 cases the head was in the persistent occipito posterior position, and in 3 of these the head was delivered in the occipito anterior position after rotation, and in 9 in the face-to-pubes position. Lower segment Caesarean section was carried out 8 times, in one case the presentation being a breech. A destructive operation was carried out in 6 cases. Cleidotomy was necessary 3 times. There were 3 cases in which delivery by the forceps failed, 2 of which required a destructive operation. Altogether there were 43 cases in which at the time of interference the head was either transversely arrested or in the persistent occipito posterior position, or in other words, in over two-thirds of all cases there was defective rotation of the head. Rings were present in 3 cases, and in 10 cases there were signs of an intrapartum infection, and in 2 of these gas was present. Recent radiological research has shown the influence of abnormalities of pelvic architecture on the mechanism of labour, and we have noted at Walton Hospital that the android pelvis is often found in cases in which transverse arrest of the head occurs, and the anthropoid pelvis in cases in which delivery of the head in the occipito posterior position takes place. That this is not the only factor, however, is shown by the fact that in 2 patients who required to be delivered by the forceps for a non-rotated head and who subsequently became pregnant, a normal delivery of a large child took place. External version was carried out during pregnancy in 3 cases.

The mention of the method of delivery gives but little idea of the difficulty of carrying it out in these cases. Most commonly, as has been shown, we are dealing with a high transversely arrested head, the so-called persistent occipito posterior of the textbooks. The head is big and hard. Manipulations are difficult, owing to the rigidity of the vulva and vagina and the contraction of the pelvis. Delivery without an episiotomy or extensive laceration and trauma is impossible. The head is

big and hard. The post-mature foetus stands the strain of labour badly, and the placenta has already passed its optimal maturity. The head does not mould well, and the risk of tentorial tears if the forceps is applied to it in the transverse position is very great. Kielland's forceps, which is of great value in this complication, was only noted as being applied once.

The 3rd stage of labour showed complications in relatively few cases, considering the high rate of interference and the slowness of the 1st and 2nd stages. Manual removal of the placenta, however, was carried out 3 times, this being about 10 times the usual rate. Otherwise serious haemorrhages were not specially noted. The placenta was described as being calcareous in 19 cases, and it would seem generally as though the calcareous placenta separates easily. The placentas also tended to be large, and with a high weight relative to that of the foetus. As already noted, manual removal was necessary in 2 of the cases in a subsequent pregnancy.

As might be expected when labour is so long, intra-partum infection so frequent, and interference and laceration the rule, the puerperal morbidity is high. The puerperium was described as being morbid or complicated in 38 cases, or in well over one-half. The usual cause was infection of pelvic origin, or of the wound in cases of Caesarean section. There were 2 cases of septicaemia, due respectively to staphylococcus aureus and bacillus coli; both patients recovered. Paralytic ileus was a marked feature in 3 cases. Goodall, in his description of the inertia syndrome, has called attention to the distension of the colon that may be obvious during labour. In one recent case, death occurred following Caesarean section from volvulus of the pelvic colon. There was one case of puerperal mania in addition to one case of mania in the 3rd stage of labour, and one case of massive collapse of the lungs. Phlebitis occurred twice. There were 3 cases of mastitis. The question of milk secretion in the puerperium is of interest both physiologically and clinically, but unfortunately the notes are lacking in information on this point. In only 3 cases was milk secretion referred to, and in these it was described as being inadequate. It is my impression, however, that in these patients the milk secretion is much below average. Feeding is difficult, both for this reason and on account of the poor general condition of mother and baby after delivery. There was a maternal death, which will be mentioned in detail later.

The babies. There was a striking difference in the sex incid-

ence of the 62 babies, there being 43 males and only 19 females. Out of 62 babies, 21 were stillborn and 4 died, a foetal mortality of no less than 40 per cent. Post-mortem examinations were carried out in 17 of the stillbirth cases. Nine babies showed tentorial tears, and 5 were macerated. There was one spina bifida. Reference was made in the post-mortem records of 13 cases to the epiphyses in the region of the knee, and in 4 of these the femoral epiphyses were present, and in 9 both femoral and tibial epiphyses. In one baby the femoral epiphyses were described as being "very large." Of the 4 neonatal deaths, one was due to a staphylococcal infection, and in another a ventricular haemorrhage was found post-mortem. Post-mortem examinations were not carried out in the other two babies, and one is described as having had "convulsions."

Of the babies that survived, many showed a large caput succedaneum and considerable moulding. Asphyxia at birth and signs of cerebral irritation in the first few days were common. There was one fractured clavicle, and one case of Erb's paralysis. The enormous risk to the foetus in this condition is, therefore, obvious.

The average weight in 61 of the babies in whom the weight was known was 8 pounds 3 ounces. This compares with an average weight of the babies in 50 primiparae at Walton Hospital of just under 7 pounds. There were 3 babies weighing 10 pounds, 10 of 9 pounds, and 2 of 5 pounds.

Case histories. Three examples of the condition may be mentioned in more detail.

(1) Primipara, aged 26, Jewess. This patient, who was very obese, was admitted to hospital as an emergency, 31 days after the expected date of delivery, and after being in labour for 8 days. On admission her temperature was 101°F., pulse-rate 140, the cervix half dilated, and the foetal heart sounds absent. A craniotomy was carried out, and later a manual removal of an extremely calcareous placenta. The patient continued to be in a state of shock in spite of treatment, and died 24 hours later. A post-mortem was not obtained. This was the only death in the series.

(2) Primipara, aged 28. This patient was stout and of masculine appearance, and was first seen on the district after being in labour for 3 days, and in the 2nd stage for 5 hours. Under anaesthesia there was found to be a very narrow pubic angle and a grossly contracted pelvic outlet, so that the hand could hardly be inserted into the pelvis. With great difficulty

and prolonged traction a baby weighing 5 pounds was eventually delivered in the face-to-pubes position by axis-traction forceps. The baby was resuscitated with difficulty. The mother became maniacal in the 3rd stage, and after 2½ hours a manual removal of the adherent placenta was carried out. The mother was subsequently very ill with sepsis and the baby with a discharging ear and scalp wounds, but both were well when seen 6 months later.

(3) (Not included in the above series.) Primipara, aged 30. This patient had a long history of dysmenorrhoea, scanty periods and amenorrhoea. There was contraction of the pelvis. Conception occurred during an intensive course of endocrine therapy. Signs of toxaemia appeared in late pregnancy. At the onset of labour there were slight pains for over 3 days, but in spite of stronger pains for over 24 hours the head remained high and there were signs of foetal distress. A lower segment Caesarean section was carried out, and a male baby in the right occipito posterior position weighing 8 pounds 4 ounces was delivered. Apart from mastitis in the puerperium, the mother made good progress, and the baby also. The husband said that his wife's mental outlook had been enormously improved by the pregnancy. At the same time that she was in hospital, a sister in another part of the country with a similar history of amenorrhoea died following a Caesarean section after attempted delivery by the forceps had failed. A third sister who had been married 3 years had not been pregnant.

Summary of clinical features. The clinical picture of this syndrome may now be reviewed. We are dealing with primigravidae late in the reproductive era and in whom fertility is low. They tend to be short and obese, and with male characteristics. The menstrual history is irregular, the pelvis small and deformed, the vagina narrow and the pelvic floor rigid. There is a high risk of toxaemia occurring and progressing to eclampsia. Pregnancy is prolonged, and the placenta calcareous. The membranes rupture early, pains are weak though distressing, and dilatation of the cervix is slow. The head fails to rotate anteriorly, and interference and lacerations are the rule. There is a high risk of intra-partum and puerperal infection. The baby, which is more commonly of the male sex, is large, and stands the strain of labour badly. Its head is large and does not mould well. There is a high risk to it from trauma and infection, both in labour and in the neonatal period, and breast-feeding is poor.

It will thus be seen that this syndrome provides us with some

of the most formidable cases it is possible to meet with in obstetric practice. Failure to appreciate its importance may lead to tragedy in the life of the woman and her home, whereas successful conduct of the case may provide the greatest family happiness, and may completely alter the patient's mental and physical life. We owe much to De Lee and the Chicago school of obstetrics for drawing our attention to this syndrome.

It must be realized that the picture just drawn, like all clinical pictures, is a composite one, and that patients will by no means show all the features mentioned. In compiling this series, however, I have endeavoured to include only those patients who have shown a combination of many features of the syndrome, and have excluded a considerable number who only presented a few of them.

It must also be appreciated that many of the complications to the mother, such as severe infection, or to the baby, such as cerebral haemorrhage, are complications which may occur in any long or difficult labour. The chance of these occurring, however, is much greater when several of the factors responsible are present, such as post-maturity, early rupture of the membranes, inertia and disproportion, as is the case in this syndrome. It must also be admitted that many of these late complications are the result of failure to recognize the condition at an early stage and to carry out other treatment.

Diagnosis. This is seldom difficult, once the features of the syndrome have been appreciated, if a complete history is taken and a full examination made. The findings at the onset of labour should make the diagnosis more certain, and it is important that there should be no delay in recognition at this stage. Some assistance as to pelvic shape and the existence of disproportion may be obtained from radiographs, and these may help us to forecast the mechanism of labour and the technique required in delivery, as has been shown by Caldwell and Molloy.

Prognosis. The great immediate risks to mother and baby are obvious from the above figures, although the results would have been greatly altered by a more extended use of Caesarean section. The later results, however, to the patient must also be borne in mind. A prolonged labour with much sepsis and laceration will leave permanent organic damage. The distant results of an intra-partum infection with gas-forming organisms are apt to be particularly serious. This grave complication is very liable to occur with the factors of early rupture of the membranes,

intra-partum death of the foetus and interference which are so frequent in this condition, and we have now had 3 patients at Walton Hospital in whom this complication has been followed by superinvolution of the uterus and obliteration of the uterine cavity.

In addition, moreover, the mental damage in these patients must be great if the baby has not survived, and especially if the patient realizes that her further chances of pregnancy are small. On the other hand, a successful pregnancy with a living and healthy child must greatly improve the patient's mental outlook, and possibly also improve her physical health by stimulation of the endocrine system, as may happen in Simmond's disease if pregnancy occurs.

Aetiology. Most of the authors who have referred to the aetiology of this condition consider it to be of pituitary origin, but there is little information available about the exact mechanism at work. The features of obesity, genital hypoplasia and amenorrhoea found in Fröhlich's syndrome, or dystrophia adiposogenitalis, are usually considered to be due to decreased secretion of the anterior lobe. On the other hand, we know that in pregnancy toxaemia and eclampsia, which are so common in this condition, there is evidence of increased secretion of the pressor substances of the posterior lobe and also of prolan, although this is apparently of placental origin. There is also evidence that overgrowth of the foetus and prolonged pregnancy, which are so frequent in this condition, may be produced in animals by injection of prolan. Malpas[9] has pointed out that many of the features of this syndrome are also present in treated diabetics in labour, and it is now believed the pituitary gland plays an important part in the pathology of diabetes. Beyond attributing an important *rôle* to the pituitary gland, and especially the anterior lobe, in this syndrome, it does not seem possible to go further in the light of our present knowledge, or to use a rational endocrine therapy. So far we have not found oestrogenic substances to be of great value in inducing labour in these cases or in treating the inertia often present, and in other cases of toxaemia we have not obtained the good results that have been reported with progesterone.

Treatment. The guiding factor in all treatment must be the knowledge that the pregnancy under consideration may be the only one that the patient will ever have, and the relative value of the foetal life must, therefore, be placed very highly. The enormous risks to the foetus of vaginal delivery in these cases

should incline us, therefore, towards delivery by Caesarean section. If the expected date of delivery is long past, on no account should a mechanical induction be carried out, as the uterus in these cases is very difficult to stimulate into action, and the risk of infection is great. If pregnancy is extremely prolonged, or clinical and radiological examination show signs of a very large or well ossified foetus, then Caesarean section should be carried out before labour starts.

The difficulties are greater when the diagnosis is not made till late in labour. We may then find that we are dealing with a patient who has been in distressing labour for some days, and who is getting exhausted. The membranes have long been ruptured, and signs of intra-partum infection and foetal distress are appearing. The cervix is only partly dilated, the head is high, the caput succedaneum is difficult to determine, the occiput is probably lateral or posterior. We are then dealing with one of the most serious types of case in obstetric practice. Caesarean section, even of the lower segment variety, carries a high risk from infection. Vaginal delivery through an incompletely dilated cervix of a large baby with a hard, high head is difficult and dangerous. The dangers will only be increased by waiting, and the foetus may die from asphyxia and infection. Speaking of the difficulties of delivery, De Lee remarks "Often, upon labour's completion, one feels that if these could have been foreseen, Caesarean section would have been a better choice at the beginning."

On reviewing the cases in this series, I think that in at least another quarter of the patients Caesarean section would have been better treatment than that carried out, though many of them were not seen till late in labour or even after unsuccessful interference, when the ideal treatment could not be carried out. The lower segment operation has now been shown to have a very low risk even in cases in which there is some degree of infection present, and we now have a powerful new weapon against sepsis in our hands in the sulphonamide group of drugs, so that its scope could probably be extended with safety. An important practical point in performing the operation has been stressed by Walsh,[10] who has found that the lower segment does not form well in this condition, even late in labour.

In those patients in whom Caesarean section is judged unnecessary or unsuitable, there is often difficulty in deciding the optimal time for vaginal delivery. On the whole I think it is probable that early delivery has fewer risks for the foetus in suit-

able surroundings and in skilled hands. This means, however, one of the most difficult and dangerous operations in the whole of obstetric practice. The head is high, and lying transversely or with the occiput in the hollow of the sacrum. The vagina and pelvis are cramped, and manual rotation is usually impossible. The classical forceps can only be applied with an antero-posterior grip on the head, which carries a very high risk of tentorial tears. In such cases the Kielland forceps is very valuable, once its use has been mastered, as it obtains a safe grip on the sides of the head. The blades can usually be applied with more safety by making them both wander round the head instead of by the classical method of rotating the anterior blade inside the uterus. There should be no hesitation in carrying out an extensive episiotomy on one or both sides in these patients, as a slow delivery over the perineum may result in the death of a foetus already subjected to grave risk. The episiotomy, however, should not be done too early, as sometimes there is considerable bleeding. If the occiput is in the hollow of the sacrum, a deliberate face-to-pubes delivery should be carried out. All preparations for treating foetal asphyxia should have been made, and vitamin K should be administered to the baby as a routine practice after birth, as there is now evidence of its prophylactic effect against neonatal haemorrhage.

Once the foetus is dead, craniotomy should be carried out. Perforation of the head is usually difficult, owing to the amount of ossification, and the head does not collapse well if it is extracted without crushing by the obstetric forceps. Much greater difficulty is often experienced in the delivery of the shoulders, which are relatively very large in these big babies. Cleidotomy is also difficult, owing to the thickness and marked ossification of the clavicle, and a better operation is to carry out a division of the ligaments of one or both sterno-clavicular joints after reaching them subcutaneously from an incision made higher up in the neck with the scissors.

If gas is present at the time of delivery, or if there are other signs of a gross intra-partum infection, the immediate carrying out of repair of lacerations or episiotomies is questionable. More recent experience, however, has shown that the local application of sulphonamide powder before suture has some promise. There is also evidence now that the use of these drugs by mouth may be of some prophylactic value against gas infections.

Mention is made of destructive operations as they were necessary in several cases in the series, and they are often very dif-

ficult. They can only be considered, however, a great obstetric tragedy in these cases.

Summary

The findings in a series of 62 cases of the "dystocia dystrophia syndrome" of De Lee have been described, and the importance of further recognition and study of this condition is urged.

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Splenic and Renal Aneurysms Complicating Pregnancy

BY

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RUPTURE of an aneurysm of the splenic or renal artery is of rare occurrence during pregnancy but there is a definite relation between the two conditions. The following 4 cases admitted to this hospital during the past 10 years are, therefore, of unusual interest.

CASE 1. SPLENIC ANEURYSM.

The first patient was admitted when 32 weeks pregnant. She was aged 30 and had had 2 previous normal pregnancies. She had been apparently well until 4 hours before admission, when she collapsed with sudden acute abdominal pain associated with vomiting and rapid pulse-rate. She was very pale and the clinical picture was one of haemorrhage. The urine was loaded with albumin, but there were not any other clinical signs of toxaemia, and vaginal haemorrhage was absent. On examination of the abdomen, extreme tenderness and distension in the epigastric region were noted. The height of the uterus corresponded with the period of amenorrhoea, and from its consistence did not suggest concealed accidental haemorrhage. She was not in labour. Her condition became rapidly worse and she died 2 hours after admission. About 40 minutes prior to death she had a convulsive seizure, which did not suggest eclampsia, epilepsy or hysteria. The post-mortem findings were as follows:

The splenic artery had a rupture near the hilum of the spleen; this rupture was of several days' standing and was surrounded by a small false aneurysm, the walls of which consisted of dense old blood clot. Gross haemorrhage from this aneurysm had occurred very recently into the pancreas and retroperitoneal tissues, and also into the lesser peritoneal sac. The blood had spread from here through the foramen of Winslow into the general peritoneal cavity, which contained much clot in its upper part, and about 500 c.c. of fluid blood.

There was a recent infarction of almost the whole spleen, and also of a large area in the centre of the right lobe of the liver. Early atheroma was present in the ascending aorta. The uterus contained a 32 weeks' foetus. The other organs were healthy but anaemic.

CASE 2. SPLENIC ANEURYSM.

The second patient was a primigravida aged 30. She had been admitted to the antenatal wards on two occasions during pregnancy suffering from hyperemesis, which appeared to be of neurotic origin as it ceased almost immediately she was admitted to hospital. The blood-pressure at that time was 120/80. Prior to her second admission she had vomited some dark green material, and there was slight ketonuria, but no nystagmus or dehydration.

Her final admission to hospital was when she was 31 weeks pregnant. On the day before, she fainted three times and complained of severe pain in the abdomen passing through to the back. She also had epistaxis, but there was not any vaginal haemorrhage. On admission she looked pale and ill and her tongue was dry and coated. The blood-pressure was 180/90 and there was a trace of albumin in the urine, but oedema was absent. The uterus was hard and tender on palpation. Clinically the condition suggested concealed accidental haemorrhage. Despite alleviative measures, she was much worse by the next day and vomited several times. The whole abdomen became tense and tender, and the patient collapsed. Examination of the abdomen now suggested the presence of intra-peritoneal haemorrhage, and the provisional diagnosis of concealed accidental haemorrhage was thus open to doubt, since it is unusual to find intra-peritoneal haemorrhage of any severity in such cases. Laparotomy was performed. The peritoneal cavity was full of blood with a large amount of dark clot in the left hypogastric region. The uterus did not have the appearance associated with concealed accidental haemorrhage. A macerated 7 months' foetus was delivered by hysterotomy, and after the uterus had been sutured it remained flabby from loss of retractile power. A search for the source of the haemorrhage was made in the left side but the bleeding point could not be located. As fresh haemorrhage had apparently ceased, and the patient was in a very parlous condition, the abdomen was closed. After operation a transfusion of 800 c.c. of blood was given and the patient rallied.

She improved somewhat the following day although vomiting continued, but she had a relapse on the 3rd day after operation, and died with evidence of recurrent internal haemorrhage. The post-mortem findings were as follows:

The splenic artery had a saccular aneurysm about 2 cm. in diameter in the substance of the pancreas, 8 cm. from the spleen. This aneurysm was obviously of rather old standing. Its walls were thick and smooth and resembled ordinary arterial wall; the cavity contained a moderate amount of white thrombus. It had ruptured first into the pancreas so that almost the whole left half of this organ was replaced by recent blood clot. The haemorrhage had then torn through the capsule of the pancreas upwards into the lesser peritoneal sac, which was distended with fresh clot. The general peritoneal cavity contained about 500 c.c. of blood which had escaped through the foramen of Winslow.

All the other arteries were healthy, and the viscera were normal although anaemic. The anterior pituitary was necrosed. The Caesarean section

incisions in the abdominal wall and uterus were beginning to heal satisfactorily.

Microscopically the wall of the artery was normal up to near the mouth of the aneurysm where the media showed some oedema and fibrosis; the whole arterial wall then faded rather quickly into the aneurysm wall. This consisted of a thick layer of fibrous tissue with a moderate amount of elastic tissue, that showed at the surface a slight condensation towards an internal lamina. There were a few large atheromatous plaques in the aneurysm. Near the point of rupture there were occasional polymorphs and a few minute groups of lymphocytes in the tissue round the aneurysm, but these all appeared to be secondary to the aneurysm. Lesions suggestive of polyarteritis nodosa, syphilis or rheumatism could not be found, and the artery itself was not atheromatous.

CASE 3. RENAL ANEURYSM.

The third patient, aged 24, 5-para, was admitted when 36 weeks gravid. Previous pregnancies had been normal. She had been well throughout this pregnancy until 5 hours before admission, when she developed severe pain in the left loin, accompanied by faintness and collapse. The pain was at first intermittent, but later became constant though less severe. The patient looked pale and shocked. The left flank was tender, and dullness to percussion extended anteriorly almost to the mid-line. The child presented as a vertex but the foetal heart could not be heard. Laparotomy was performed and a very large retroperitoneal haematoma was found in the left flank, extending from the pelvis to the diaphragm. A stillborn child was delivered by Caesarean section and, thereafter, an attempt was made to find the source of haemorrhage by incising the haematoma. Bleeding, impossible to control, was found to be welling up from the left flank, and accordingly packing of the haematoma was resorted to. Blood transfusions were given during and after operation but the patient died about an hour later.

The post-mortem findings were as follows:

The left renal artery had two saccular aneurysms each about .2 cm. in diameter; one was about 3 cm. from the hilum, and the other just at the hilum of the kidney. They had thick smooth walls and appeared to be of long standing. The aneurysm furthest from the kidney had leaked, giving rise to a recent false aneurysm of about the same size. This false aneurysm had ruptured into the retroperitoneal tissues, producing an enormous haematoma which extended from the diaphragm down to the pelvis, and from the aorta out to beyond the kidney. The peritoneal cavity contained much free blood.

All the other arteries were healthy, and the viscera were normal apart from anaemia. There was a fresh Caesarean section incision, and the lower part of the haematoma near the pelvis had been opened and packed with gauze. An old appendicectomy scar was also present.

Microscopically the wall of the artery was normal up to the mouth of the aneurysm where the aneurysmal wall began suddenly. This consisted of a thick layer of fibrous and elastic tissue with a fairly well-developed internal

elastic lamina. Several large patches of atheroma were present, and one showed some superficial ulceration with thrombus formation on it. There were occasional polymorphs in the tissue round the aneurysm; these appeared to be spreading from the blood clot, and to be secondary to the rupture. Lesions suggestive of polyarteritis nodosa, syphilis or rheumatism could not be found, and the artery again did not show any atheromatous changes.

CASE 4. RENAL ANEURYSM.

The fourth case is rather less satisfactory as the post-mortem examination was not sufficiently detailed, and it is thus impossible to confirm the diagnosis absolutely.

The patient was aged 28, 2-para. She was 29 weeks pregnant, and had a history suggestive of a previous pregnancy albuminuria. A week before admission she developed oedema of the feet and headaches, and 24 hours before admission she developed severe backache, and was pale and restless. Abdominal examination suggested free fluid in the peritoneal cavity. Her blood-pressure was 145/110. An hour after admission she had a miscarriage of a macerated foetus, and thereafter complained bitterly of pain in the left side, but there was not any tenderness or rigidity. Her condition rapidly deteriorated and she died two hours after delivery.

A cursory post-mortem examination showed a very large retroperitoneal haemorrhage in the left flank, centred about the hilum of the kidney, and extending from the diaphragm to the pelvic cavity. The left kidney was completely embedded in the haematoma, and it was considered that the renal artery was the source of the haemorrhage.

DISCUSSION

Pathology. The incidence of splenic aneurysms found at post-mortems in general hospitals is about 0.05 per cent, whereas the incidence of all types of aneurysms is 1.26 per cent.

The literature contains detailed records of 94 cases of splenic aneurysm and of 66 cases of renal aneurysm. The cases of splenic aneurysm up to 1929 were analysed by Bertrand and Clavel[1] and by Anderson and Gray,[2] whose review is carried up to the end of 1937 by Machemer and Fuge;[3] subsequent cases are recorded by Bauer and Appelbach,[4] Gunther,[5] Ostling,[6] Guy,[7] Matronola,[8] Pasternack and Shaw,[9] Sperling,[10] and Seids and Hauser.[11] The cases of renal aneurysm up to 1931 were analysed by Mathé[12] and by Gerard;[13] subsequent cases are recorded by Wagener,[14] Wesson and Fulmer,[15] Loughnane,[16] Fircks,[17] McKay,[18] Kastner,[19] Smith and Walkling,[20] Cohen and Steinbach,[21] Ostling,[6] and McClelland.[22] The various hypotheses which have been put forward to account for the aneurysms are amply discussed in the previous reviews, but there are two

points which have not received so much attention as they merit, namely, the relation of the aneurysms to the sex and age of the patients, and the relation of the aneurysms to pregnancy.

The table showing the sex and age incidence is made up from the cases in the literature and includes the present four. The age given is that at which the aneurysm was diagnosed. In nearly all the cases it is the age at which the aneurysm ruptured and caused the death of the patient. There are rarely any symptoms before the rupture occurs, so that the previous duration of the aneurysm cannot be determined accurately. The histological appearances suggest, however, that the usual duration is of several months or even years.

Age	Males	Females	
		Total	Pregnant
SPLENIC ANEURYSMS.			
0 to 15	1	0	–
16 to 25	2	5	5
Young adult	0	2	2
26 to 35	5	17	7
36 to 45	4	10	2
46 to 55	7	8	–
56 to 65	8	9	–
66 to 75	2	6	–
Unstated	3	1	–
RENAL ANEURYSMS.			
0 to 15	2	0	–
16 to 25	4	2	2
Young adult	4	1	0
26 to 35	6	2	2
36 to 45	5	2	0
46 to 55	7	8	–
56 to 65	4	9	–
66 to 75	4	1	–
76 to 85	2	1	–
Unstated	1	1	–

It will be seen from the table that, after the age of 45, there is not any significant difference in the sex incidence of the aneurysms of either artery. Thus in these older patients there were 20 males and 24 females with splenic aneurysm, and 18 males and 20 females with renal aneurysm. Before the age of 45 there is, however, a very striking sex difference in each type. With

splenic aneurysms there is a great preponderance of females, namely, 34 females to 12 males. On the other hand, with renal aneurysms the position is reversed, there being 21 males to 7 females. With our present knowledge, a really adequate explanation cannot be offered for this peculiar tendency of splenic aneurysms to occur in young adult females, and of renal aneurysms to occur in young adult males. Histological examination does not give any clue to their aetiology in the vast majority of cases.

The second point of interest is that half of these aneurysms which occurred in women from 15 to 45 years old are associated with pregnancy. The incidence is much greater than can be accounted for by mere coincidence, as the average woman is not pregnant for more than two, or at most three, years during the child-bearing period of 30 years under review. It is of course possible that the higher incidence credited to pregnant patients may be due to the fact that a case occurring during pregnancy is of unusual interest, and is perhaps more likely to be recorded than one in a non-pregnant woman. This explanation, if true, should apply equally to cases in early and late pregnancy, whereas, as is shown below, practically every case associated with pregnancy occurs in late pregnancy. It would therefore appear that the high incidence in pregnancy is probably a real one, and that, though these aneurysms are rare, pregnancy is a definite factor in precipitating their rupture. There is not yet sufficient evidence to decide whether pregnancy plays a part in their causation.

The following list gives the cases in pregnancy reported in the literature, including the present series. It will be seen that all but one of the patients were over 28 weeks pregnant, and that most were at term or near it. This immediately raises the question of whether there is a relation to the toxaemias of late pregnancy, in view of the possibility that hypertension might lead to rupture of an aneurysm. Two of the present cases had a hypertensive toxaemia during the pregnancy, but such a history is not found in any of the other published cases. The association with the later stages of pregnancy must thus be left at present as an unexplained fact. The parity of the patient does not seem to be of significance; the distribution of parities among the published cases is not different from that among any series of ordinary obstetric autopsies. This negative finding suggests a lack of relation to those conditions which are most often met with in primigravidae, such as eclamptic toxaemia, or to those

which are most common in advanced multiparae, such as concealed accidental haemorrhage. Age on the other hand appears to be an important factor; all the aneurysms in women under 25 are associated with pregnancy, but only a half of those in women from 26 to 35, and only a sixth of those in women from 36 to 45, are in pregnant women. This is probably only another aspect of the influence of pregnancy in leading to rupture of aneurysms. Older women develop such rupture without pregnancy; younger women, on the other hand, are unlikely to rupture an aneurysm unless they are pregnant.

SPLENIC ANEURYSMS IN PREGNANCY.

Reynolds,[23] and van Rooy,[24] aged 28, at term.
Smith,[25] aged 35, at term.
Wesenberg,[26] 4-para, aged 32, 33 weeks.
Lundwall and Gödl,[27] primipara, aged 24, at term.
Yolland,[28] primipara, aged 27, 18 weeks.
Saenger,[29] 9-para, aged 40, 33 weeks.
Remmelts, R.,[30] 9-para, aged 38, at term.
Remmelts, E.,[31] no details available.
Mayer,[32] 3-para, aged 27, at term.
Bauer and Appelbach,[4] aged 24, 35 weeks.
Heuveldop,[33] 2-para, 35 weeks.
Sered and Steiner,[34] 3-para, aged 30, at term.
Ostling,[6] primipara, aged 21, 7 days post-partum.
Guy,[7] aged 25, 28 weeks, from size of foetus.
Present case 1, 3-para, aged 30, 32 weeks.
Present case 2, primipara, aged 30, 31 weeks.

RENAL ANEURYSMS IN PREGNANCY.

Chisholm,[35] 2-para, aged 28, 32 weeks.
Ostling,[6] primipara, aged 24, at term.
Present case 3, 5-para, aged 24, 36 weeks.
Present case 4, 2-para, aged 28, 29 weeks.

Diagnosis and Treatment.

The chief difficulty in the diagnosis lies in the rarity of these aneurysms. In a few exceptional cases, an unruptured aneurysm, which has caused slight symptoms of indigestion, has been recognized clinically or radiologically and treated successfully by operation. There is also a possibility, in an aneurysm which ruptures in two stages, of recognizing the condition in the almost symptomless stage that lasts a week or two after the first small rupture. The usual position, however, is that the patient is first

seen after gross rupture has occurred. There have not been any symptoms until a sudden onset of severe pain occurs in the upper abdomen or left side, sometimes radiating to the left shoulder or back. This is followed rapidly by collapse of the patient, which may mask the acute anaemia that develops. In any patient, male or female, a wide variety of diagnoses may be made at this stage, such as perforation of a peptic ulcer, acute haemorrhagic pancreatitis, acute intestinal obstruction, or, in a woman, ruptured ectopic pregnancy. In a patient advanced in pregnancy, the most usual diagnosis is concealed accidental haemorrhage, though rupture of a previous Caesarean scar, or rupture of an advanced abdominal pregnancy, may be considered. The epigastric pain may suggest a severe pre-eclampsia. Sooner or later, however, indications of internal haemorrhage are found and it becomes clear that an upper abdominal emergency has occurred, and that laparotomy is required. When this is performed, the surgeon finds a state of affairs that fills him with a sense of surgical perplexity. If it is a splenic aneurysm that has ruptured, the peritoneal cavity is full of blood clot, and of fresh blood welling up from some indefinite upper abdominal source which is actually the foramen of Winslow. A large haematoma in the region of the pancreas may possibly be recognized through the blood. If it is a ruptured renal aneurysm, gross free blood is not found in the peritoneal cavity, but a huge haematoma occupies the whole of the flank from diaphragm to pelvis.

The treatment which is suggested here is based on considerations following experience of these disasters, in which the ideal line of treatment was not appreciated at the time. The primary requirement is that the surgeon must, at the laparatomy, be actively aware of the probable diagnosis. He must first exclude any obstetric cause for the haemorrhage. The next step is a rapid Caesarean section to clear the field. The foetus need not be considered as it is always dead and usually macerated.

If there is gross intra-peritoneal haemorrhage coming from the upper abdomen, rupture of a hepatic or superior mesenteric aneurysm should be quickly excluded. The lesser sac must now be opened by splitting the great omentum just below the stomach, and an attempt made to locate roughly where the bleeding originates. Digital compression of the splenic artery may assist at this stage. The splenic artery must then be ligated at a reasonable distance proximal to the apparent bleeding point; this ligature may have to be applied in a blind manner in the

haematoma. Unless the condition of the patient permits of excision, the spleen can be left to undergo aseptic atrophy; this has been done successfully by certain surgeons.

If there is a large haematoma in the flank, the two conditions to be excluded are lateral rupture of the lower uterine segment and rupture of an aortic aneurysm, although this latter condition is extremely rare in pregnancy. An incision of the haematoma in an attempt to find its source should not be made; this produces such haemorrhage that immediate packing has always to be resorted to in order to avoid an operative disaster. Instead, the position of the renal pedicle should be ascertained and a clamp applied to it near the aorta. This procedure may have to be done blindly in the haematoma. The pedicle can then be ligatured and the kidney excised. As much of the blood clot as possible should be removed from the retroperitoneal tissues, as this will lessen the risk of sepsis.

It is to be emphasized that a probable diagnosis is sufficient basis for drastic action of this kind to be taken without any hesitation. A ruptured aneurysm is an occasion for unusual and even heroic surgery, since the outlook for the patient is quite hopeless if a real attempt is not made to stop the haemorrhage.

During and after the operation, massive blood transfusion is indicated. Even if the operation is successful, there is danger of subsequent sepsis in the haematoma, or of anterior pituitary necrosis. The prognosis must, therefore, always be guarded. Every case so far reported in pregnancy has been fatal, but there is reason to hope for more success in the future if, at operation, the condition is recognized and dealt with on the lines suggested.

Summary

Two cases are reported of rupture of an aneurysm of the splenic artery, and two cases of rupture of an aneurysm of the renal artery. These all occurred during the later months of pregnancy.

A review of the literature shows that splenic aneurysms occur with particular frequency in young adult women, whereas renal aneurysms are commonest in young adult men.

Women are especially prone to have such ruptured aneurysms in the later stages of pregnancy, for some reason unknown. This involves the splenic much oftener than the renal artery.

If a woman, in the later stages of pregnancy, develops sudden upper abdominal pain and is found to have much free blood

in the peritoneal cavity, not due to an obstetric complication, the possibility of a ruptured splenic aneurysm must be borne in mind. A large haematoma in the kidney region should suggest a ruptured renal aneurysm.

The only method of dealing with this catastrophe is rapid recognition of the condition and heroic surgery. The affected artery must be ligated proximal to the aneurysm, and, if possible, the spleen or kidney should be removed.

NOTE

While this paper was in the press, four further reports of splenic aneurysms in pregnancy were found. In the first two of these splenectomy was performed and the patients recovered. [36, 37, 38, 39]

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Notes on a Case of Secondary Abdominal Pregnancy

BY

E. R. WIDE

Belgian Congo

Bómóló Anne. Bosulu; approximate age 30. Chefferie Bongilima; Baringa, Basankusu. Belgian Congo. Tribe, Mongo (Bantu).

A rather small medium built negress presented herself at Baringa on February 27th, 1941, complaining of a large abdominal swelling of several months' duration.

Previous history. One normal labour previously about 6 years ago, child alive and well. No miscarriages. No history of venereal disease. No history of yaws.

History of present condition. Amenorrhoea for about a year. Vague abdominal discomfort from time to time not localized. She had noticed her abdomen getting large and had thought herself to be pregnant and had attended a Mission Dispensary 120 miles away where she hoped to have her baby.

Condition on examination. General appearance good, fairly well nourished, no oedema; breasts normal. Abdomen: a large round tumour practically filled the abdomen, reaching 3 or 4 inches above the umbilicus. Abdominal wall seemed free on the tumour. Dull in front, resonant at flanks, no sign of free fluid. *Per vaginam*: uterus palpable apart from tumour, slightly enlarged, body and cervix rather softer than normal. No sign of haemorrhage or discharge.

Pre-operative diagnosis—ovarian cyst.

Urine: 1030; albumin present, this disappeared after rest in bed.

Operation: Performed under heavy stovaine spinal analgesia March 5th, 1941. Abdomen opened by a 10 inches left paramedian incision. Large tumour adherent to peritoneum all over its anterior surface. Dark greenish colour with layers of lymph on the outside of the tumour.

The tumour was attached to the soft enlarged uterus at the left cornu. It had a fairly large pedicle with large vessels, and many adhesions to the great omentum above. The tumour was

removed intact without undue difficulty. When opened a fully developed male child was discovered.

The placenta was not evident, but had probably been situated at the left superior portion of tumour where there were considerable adhesions to the great omentum. The abdomen was closed in layers. Drainage was provided because of the many adhesions separated. The drainage tube was removed after 24 hours.

Subsequent inquiry elicited the information that the woman had felt movements up to Christmas 1940 when she had pains for a whole night and thought she had commenced labour. There was some haemorrhage *per vaginam* at this time. The following day movements were no longer felt.

The post-operative period was afebrile after the 1st day and the patient was discharged well on March 24th.

Some of the Changes at the Rotunda Hospital since 1926

BY

BETHEL SOLOMONS, M.D., F.R.C.P.I., F.R.C.O.G., F.A.C.S. (Hon.)

Gynaecologist, Dr. Steevens' Hospital, Dublin; Late Master Rotunda Hospital

THE vision of Bartholomew Mosse was great when he founded the Rotunda in 1745 and made a Charter which is sound to-day. The bicentenary of the hospital is near at hand, and since the main scheme for changes in the hospital, as it exists to-day, was made during my Mastership, I find it a fitting time to give the obstetricians of the world, especially those who have taken out Undergraduate and Post-graduate courses at the Rotunda, some idea of what the present hospital is like.

I do not for a moment believe that buildings make for good obstetrics; the work done in the little concrete-floored labour wards has, I believe, never been improved. The nursing of the convalescent patients in the wards with their well-worn floors will probably not be bettered; but the comfort for the patients, doctors and nurses, in modern labour and convalescent wards is well worth the money and trouble expended.

When I was appointed Master in 1926 I was convinced that no one could be satisfied with the state of affairs, and the list of improvements, to be mentioned later, and the work now completed are a thorough justification for my dissatisfaction.

The Master of the Rotunda cannot get things done without a sympathetic Board of Governors, and there is no hospital in the world where the 'one Master or Director' system exists where the Board is more sympathetic.

In 1926 the annual expenditure was about £10,000; to-day it is about £26,000.

It was necessary to go slow with demands for improvements, for apart from everything else, since there was no money this had to be raised. The most obvious necessity was a new operating theatre. There was no X-ray department; in fact so far as I am aware the Rotunda was the first maternity hospital in Great Britain and Ireland to have such a department, although

the general hospitals in Britain used X-ray rooms in association with their maternity wards. The amount of utero-salpingography I did, and the investigation in pelvic architecture by my successor, apart from other activities, showed the necessity for this department. It seemed extraordinary, too, that there was no ward for the treatment of sick babies; nor was there a place where nurses for babies could be trained, although an average of 70 midwives were trained annually; and last, but not least, the Pathological Department had been in abeyance for some time and the work was being carried on outside the hospital.

The foregoing were a few of the preliminary problems with which I was faced, and as I was wondering how the money could be raised, the elements worried us further and a storm blew down a portion of the beautiful dome, the re-erection of which cost about £700. There were no Irish Sweepstakes then, and a committee was formed to raise funds. Believing that the necessary £10,000 or £12,000 which were immediately necessary could be raised some of the work was proceeded with but much cheeseparing had to be done, and we could not have all we wanted.

An X-ray room with modern instruments was established in charge of Dr. McDonagh; a nursery where sick babies were treated was started in charge of Dr. Brian Crichton; and a small training school for Nursery Nurses formed part of the scheme. Dr. Collis has since been appointed Paediatrician. A new floor was built on the site of the old Pathological Laboratory, for purposes of research, and Dr. Bourke was appointed Pathologist. A new wing was built comprising a much needed operating theatre, with dressing rooms, bathroom, and new sterilizing plant, on one floor, and rooms for the sisters on the lower floor. For the first time a lecture theatre which was improvised out of the old operating theatre was provided. Many other improvements were made such as a new boiler house, and electric lift. It was difficult to make new appointments to the staff because of lack of funds, but in addition to those already mentioned, a sister was placed in charge of the X-ray department in 1929; a radium consultant and a radiographer were appointed in 1932. An Honorary Almoner started work in 1931, but this part of the work was on a very modest scale. All this time we were heartbroken seeking funds. To show the extent of our poverty—in 1927 an estimate for necessary repairs was sent back to the House Committee with the remark that the work must not cost more than £300.

The collections started in 1928 realized upwards of £10,000 which was collected at a cost of £900 and this was due to untiring efforts of the Board and Committee which organized flag days, fêtes, and collections. It may be of interest to note that the first motor garage for the Master and his assistants was built in December, 1929. But still the needs of the hospital were great, and about this time the Irish Sweepstake was established. Although the hospital was originally built partly out of funds from lotteries, many members of the Board were averse to participating in anything which was in any way connected with gambling. The suggestion that the Rotunda should participate in the Irish Sweepstake scheme was brought up in March, 1930, and in November, 1930, and each time the proposal was defeated. The adversaries of the Sweep stated that they thought enough money could be raised without this participation. The Archbishop of Dublin, his wife, and many collaborators worked hard, but in spite of their splendid efforts the results were infinitesimal in comparison with the funds needed. Various suggestions were made, such as to sell the Round Room; to let out that part of the gardens abutting on the street for building; but luckily these suggestions were not carried out, and in July, 1931, a resolution was passed by 17 votes to 8 by which the hospital became a participator in the Irish Sweepstake funds. One of the most striking speeches about this time was made by a Governor who was an adversary of the Sweep because of his conscientious views against any form of gambling. He himself brought up the question and said he was against them, but he was not sure if it was wise to deprive the patients of such a benefit. He, at the same time, said he would have to resign the Board if the resolution was passed; so he was one of the valuable governors lost to the hospital. As Master, I was asked my opinion and I pointed out "that an enormous sum of money was required to keep the hospital on at least an equal footing with other maternity hospitals, and that the money must be found. Sweepstakes appeared an easy way out of the difficulty. The welfare of the patients was at stake." Once agreeing to accept contributions from the Sweepstake the rest was much easier.

In January, 1932, a list of requirements was drawn up and Mr. Hicks the architect was asked to make plans. The new Rotunda, as it is to-day, is with some slight exceptions the result of the suggestions made at the meeting and the plans drawn up by Mr. Hicks, for the Sweepstake authorities. It may be of interest to hear of this huge list:

Nurses' home for 60 nurses. Reconstruct students' quarters. New laundry. A new out-patients' department. New roof on main building. Kitchen and sculleries. New floors (maple) eight wards and returns. Repairs to floor of corridors. Repairs to garden railings. Tiled walls and tiled floors. New cooking plant. Electrification of old lift to run to basement level. Electric food lift. Equipment: X-ray, diathermy, baby incubators. General repairs to windows and doors. Repainting. Electric wiring. Reconstruction of lodges. House for head boilerman. Master's bathroom and servants' quarters. Rebuild east wall Master's house. Rebuild area walls of main building at back. Granite facing to north-west wing main building similar to work executed outside Master's dining room. Repairs to stonework throughout. Repair defective roofs, and Matron's quarters. Reconstruction of boiler house, new tall chimney and Airclar smoke eliminators. Pointing and repairs to Thomas Plunkett Cairnes' Wing. Disinfecting chamber, and shoot and lift to same. Work to Round Room buildings.

Comments will now be made:

The Nurses' Home was to be removed from the main building; a new one built on the site of the old skating rink. The new Out-Patients' department was built on the side of the Square. The students' quarters were to be pulled down, and new quarters erected. All these improvements have been carried out and are magnificent. New kitchens and sculleries were suggested, but the idea of placing them at the top of the hospital was suggested later. I do not think there are any comments to be made about the other changes.

Unfortunately, my period of office terminated at the end of 7 years according to the Charter, so I was not lucky enough to see the fulfilment of my desires accomplished *then*, but it was grand to leave the hospital and to feel that all this work would be done, as it has been with important additions, under the Mastership of Dr. Davidson, my successor, who with his building committee consisting of Mr. Eaton, Mr. Jacob, the indefatigable Mr. Hubbard Clarke in the chair, and in attendance the architect, Mr. Hicks, and his assistant, the Delap Waller representative Mr. Barry, and the consulting electrical engineer, Mr. Tweedy, are to be congratulated in every sense of the word. Needless to say, the Matron, Miss Hill, was in constant consultation.

The wards have new floors; the infants' department is a real modern infants' hospital in the Maternity Hospital. There is a splendid social service scheme. In spite of all this modernizing, the Rotunda still preserves its traditions. From the front it looks

the same! And the efforts to combat the maternal mortality; to keep morbidity at a low level; and to teach nurses, doctors and students their job, are still preserved.

The total amount received from the funds of the Sweep was approximately £220,000.

The new Master, Dr. Falkiner, will not allow the Rotunda to stand still, he knows improvements are always wanted; and a magnificent modern Lecture Theatre is already to his credit, while the Pathological and Biochemical Laboratories under Dr. Gerald Dockeray will produce results for research.

In the good days when the war is over visitors will come and see the place.

The number of extern and intern patients has increased by leaps and bounds. There are wards for obstetrical and private gynaecological "pay" patients. This is a new departure as the Master did not do private practice in the hospital in my time. The Rotunda is now an up-to-date hospital in every sense of the word where treatment and teaching can be carried on under the best conditions, and where students, unqualified and qualified, as well as nurses, can live and learn in comfort.

Bartholomew Mosse can rest in peace!

"Miseris Solamen Instituit, MDCCLVII."

Obituary

Joseph B. De Lee

JOSEPH B. DE LEE'S death is a grave loss. For long he has led American Obstetrics, and his influence has become world-wide.

Some years ago I had the privilege of his hospitality. He had an arresting appearance. Tall, slim, erect, with white hair, small bright eyes, and small pointed beard made prominent by habitual use of a white tie, he compelled attention and respect. A quickness of gesture, and a sharpness of speech betokened his alert mind. Above all, he conveyed an indefinable sense of elation, and few there were who did not come under his spell. He lived for obstetrics, and obstetrics gave him his driving force.

As a young man he faced great difficulties, and his medical education was gained at the expense of heavy debts. Soon he organized a maternity service in a poorer district of Chicago, and by dint of sheer hard work established a reputation for sound judgment, outstanding craftsmanship and originality of thought and action. Yet his progress was not easy. He faced racial opposition; he had no skill or patience with compromize; he had little sense of humour; he could not smooth the feelings of those with whom he found himself in opposition. In spite of, or perhaps because of, these characteristics he steadily rose to the first place in American Obstetrics. His textbook must now command one of the world's biggest sales.

A comparison with Whitridge Williams, for long his contemporary, is inevitable. In many ways the two men vied with each other and both produced textbooks of outstanding merit. Williams was a scientist with solid training in pathology and an encyclopaedic knowledge of obstetric literature. De Lee was a craftsman with a vast store of clinical experience. Both were leaders of thought and both introduced much of value to obstetrics. Both were controversionalists, but while Williams, as it were, wielded a sharp and heavy sword, De Lee thrust with a quick rapier.

In the two hospitals built under De Lee's guidance there are many marks of originality and, in places, of sentimentality. Two old bricks are to be seen, built into the wall at each side of the

entrance door of his first hospital. These are the bricks that had supported, over a spirit lamp, the small sterilizer that had served De Lee so long and well in his "apprentice" days at the Obstetric Dispensary. In the second—a beautifully constructed building—there are numerous floral designs on the external stonework. To those who have eyes to see, many curious obstetric devices have been cleverly introduced—a foetus *in utero*, twins *in utero*, obstetric forceps, obstetric callipers and so on. Elsewhere a colonnade is embellished with a series of scrolls that bear the names of famous obstetricians of the past. One is blank: it waits for the man who shall solve the problem of eclampsia. In the labour rooms, various proverbs and exhortations are displayed in artistic bronze lettering. De Lee was more than displeased when, for the reader's benefit, a reporter facetiously translated "*artenon vi*" and "*primum non nocere*" as "not by force but by forceps," and "the first time does not matter"!

De Lee was a great artist. Temperamental he was, no doubt —but staunch of purpose when striving after almost unobtainable perfection in his craft. To watch him conduct a delivery was an unforgettable experience. The patient was lightly anaesthetized with ethylene gas. Complete order prevailed. Not a drop of blood soiled the floor. Even when dealing with private cases his hospital residents and internes were invariably present to watch every movement. It was a rule that if any flaw of aseptic technique was detected, the onlookers must at once speak out in a loud voice. Seldom was the silence disturbed! Conservatism and radicalism were curiously mixed. Labour was allowed to progress normally, but "prophylactic forceps" was the rule for delivery. Every perineum was incised and later stitched with infinite care and precision. "Could *your* mouth ever regain its shape if you swallowed a water-melon?" he would demand of a critic—and certainly De Lee's mothers were restored to a well-nigh nulliparous state by his skilful attention. De Lee will always be known for the battle he fought for the lower segment Caesarean section. His remarkable talkie-film played no small part in winning recognition for the undoubted merits of this operation. Yet it may be questioned whether he was not somewhat economical in praise of the part played in this battle by contemporaries such as Beck of Brooklyn and Munro Kerr in this country.

During his latter years a remarkable feature of De Lee's work was the weekly meeting at which he discussed his private cor-

respondence. He was in the habit of receiving "posers" from doctors the world over; and he delighted in his *rôle* of what might now be termed a "one-man brains-trust." He was a master of incisive phrase. For many years the *American Year Book of Obstetrics and Gynecology* has owed much of its success to the penetrating editorial remarks on almost every article reviewed. His comment on the modern demand for easy and quick labour is likely to become famous—"a streamlined labour is as safe as as streamlined parachute."

De Lee's attitude to this country was always most cordial. He delighted in our medical history, and my last communication from him concerned his distress at the bombing of the College of Surgeon's Museum, and his hope that the pictures of famous obstetricians had escaped destruction. He was, I believe, a generous donor to British War Charities.

De Lee was a fighter, and he seldom lost a battle. He was an acknowledged leader, and the gap left will be hard to fill.

CHASSAR MOIR.

HERBERT SIDNEY FORSDIKE

HERBERT SIDNEY FORSDIKE studied medicine at University College Hospital and qualified in 1901—obtaining the M.D., London, in 1913, the F.R.C.S., Edin., in 1917, and the F.R.C.S., Eng., in 1920. He became Surgical Registrar at the Hospital for Women, Soho Square, in 1917, and was elected to the Honorary Medical Staff in 1919. He retired from active hospital work in 1935, after sixteen years of valuable service including five years as Chairman of the Medical Committee.

During his association with the Hospital for Women Forsdike did valuable research on the effects of radium upon living tissues with special reference to its use in the treatment of malignant disease and was awarded the Jacksonian Prize of the Royal College of Surgeons in 1922 for his essay on this subject. In 1924 he was appointed Hunterian Professor—lecturing on the same subject. From 1929-31 he examined in Midwifery for the English Conjoint Board.

Besides his appointment at the Hospital for Women, Forsdike held the posts of Gynaecological Surgeon to the Kensington General Hospital and the Princess Beatrice Hospital—and during the last war he held a temporary commission in the R.A.M.C., serving as surgical specialist at the Paddington Military Hospital.

He published a book on *Sterility in Women* in 1928 and a short *Textbook of Gynaecology* in 1932, besides a number of papers on the radium treatment of uterine haemorrhage.

Sidney Forsdike was trusted and loved by his many patients. He had great clinical experience and wisdom—his innate kindness, tolerance and keen sense of humour endeared him to his friends and colleagues alike. Unassuming, modest and energetic he never forgot the social and domestic side of life, so that for him his life was a success in the fullest sense of the word. For his devoted daughter, his many friends will feel a deep sympathy.

LEONARD PHILLIPS.

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

The Quarterly Meeting of the Council was held on Saturday, April 25th, 1942, in the College House, with the President, Professor W. Fletcher Shaw, in the Chair.

The following was formally admitted to the Fellowship, by the President:
Frank Neon Reynolds, London.

The following have been elected to the Fellowship:
William John Hunt Montgomery Beattie, London.
Calvert Merton Gwillim, London.

The following were admitted to the Membership:
Vivian Henry Barnett (R.A.M.C.)
Hubert Henry Fouracre Barns (R.A.F.)
Mary Ardelice Murray Bigby, London.
Austin Brian Concanon, London.
Mary Doreen Daley, London.
Melvin Lloyd Gaudin, Canada (R.A.F.)
Leslie Andrews Ledingham, London.
Kenneth MacIver MacKenzie, Sheffield.
Lilian Mary Norah Raftery, London.

The Annual General Meeting of the College was held on Saturday, April 25th, 1942, in the College House, with the President, Professor W. Fletcher Shaw, in the Chair.

The following were elected to Council in place of those retiring by statutory rotation:

Representatives of the Fellows:
William Gilliatt, London.
Andrew Moynihan Claye, Leeds.
Ernest Chalmers Fahmy, Edinburgh.
Charles Horner Greer Macafee, Belfast.

Representatives of the Members:
Arthur Capel Herbert Bell, London.
Hector Ross MacLennan, Glasgow.

Review of Current Literature

Director: FREDERICK ROQUES, M.A., M.D., M.Chir. (Cantab.), F.R.C.S., F.R.C.O.G.

THIS Review contains the lists of contents and abstracts of the more important articles from the journals with which the *Journal of Obstetrics and Gynaecology of the British Empire* exchanges.

The Review of Current Literature has kept the readers of the Journal in touch with current literature throughout the world; owing to the war many journals with which the *Journal of Obstetrics and Gynaecology* previously exchanged are no longer received. At the end of the year an Index of all the subjects contained in the articles of the journals reviewed is printed. Arrangements are also made to include abstracts of important articles on border-line subjects, such as Physiology, Biology, and Biochemistry.

LIST OF ABSTRACTORS

J. LYLE CAMERON, F.R.C.S.; W. E. CROWTHER, M.B.; R. H. B. ADAMSON, M.D.; B. JEAFFRESON, F.R.C.S.; P. MALPAS, F.R.C.S.; T. N. A. JEFFCOATE, F.R.C.S.; MEAVE KENNY, F.R.C.S.; JANE H. FILSHILL.

The Medical Journal of Australia

May 31st, 1941.

*Infertile marriage or sterility. A. Grant.

June 21st, 1941.

Rudimentary cervix necessitating Caesarean section. E. M. Kent Hughes.

July 5th, 1941.

Hydatidiform mole and chorion-epithelioma. A report of two cases. A. M. Hill.

September 27th, 1941.

*Haemorrhage, anaemia and jaundice in the newborn. Felix Arden.

INFERTILE MARRIAGE OR STERILITY.

A. Grant bases his paper on the findings in 225 cases investigated at the Sterility Clinic at the Women's Hospital, Crown Street, Sydney.

He assumes that 10 per cent to 15 per cent of all marriages are sterile and that among the remainder there are varying degrees of fertility. The standard

taken in this investigation of what should be considered a sterile marriage was a lapse of two years without the occurrence of any pregnancy provided that no contraceptive has been employed during that period. The term "Primary sterility" was used to indicate that the patient had never conceived and "Secondary sterility" that the patient had been pregnant once but had not become pregnant a second time.

The writer emphasizes two points. First, that the male is the causal factor in an increasing number of childless marriages during recent years, male sterility or infertility being responsible for 20 per cent to 25 per cent of cases at the clinic. Second, that it is uncommon to find one single fault operating to cause a childless marriage. There may be several factors, which are called "Infertility factors," of which one may predominate in any particular case. Of these factors the commonest in the female is obstructed Fallopian tubes and in the male azoospermia. The writer goes into careful detail in his description of the investigation of the male partner. He describes the normal semen and the characteristics of an infertile specimen, and gives directions for the collection and examination of a specimen of semen as well as the carrying out of Hühner's test. Treatment of male sterility due to azoospermia usually consists in referring the patient to a urologist for a local and general physical overhaul, followed by appropriate general treatment.

Investigation of the female partner in a sterile marriage starts with a complete gynaecological overhaul and recording of her previous medical history.

In the female the commoner factors found are (1) blocked or obstructed Fallopian tubes, (2) genital hypoplasia, tumours and malposition of the uterus, (3) tumours and cysts of the ovary and anovulation menstruation, (4) cervicitis with a sticky mucous plug, (5) infections and obstructions in the vagina—for example, fungus disease, trichomonas or intact hymen, (6) disorders of general health and especially thyroid deficiency.

Assessment of the factors involved in any case should be followed by appropriate treatment of the defect. Details of treatment are carefully outlined.

HAEMORRHAGE, ANAEMIA AND JAUNDICE IN THE NEWBORN.

Felix Arden, the Medical Superintendent of the Hospital for Sick Children, Brisbane, gives a comprehensive review of the cases observed by himself during the 14 months' period ending March 31st, 1941. The clinical material consisted of 26 cases of infants born at the Women's Hospital, Brisbane, presenting one or more symptoms of haemorrhage, anaemia or jaundice and, in addition, one severe case of haemolytic anaemia born in 1939.

As a preliminary he makes the observation that there are mild conditions of the newborn which are so common that they are termed physiological. These are (1) a haemorrhagic tendency with low prothrombin level and increased bleeding and coagulation times. (2) A tendency to the development of anaemia (*a*) from inability of the haemopoietic tissue to meet the demands of blood formation, or (*b*) from haemolysis. (3) An icteric tendency which is almost universal and which takes the form of raised serum bilirubin level or of frank jaundice.

In a large series of these physiological states all degrees of severity are

met with and eventually one reaches a point where they must be looked upon as pathological.

He tabulates his cases of pathological severity as follows:—

Physiological condition	Pathological condition	Cases	Deaths
Haemorrhagic tendency	Haemorrhagic disease of the newborn	5	1
Physiological anaemia	Anaemia of the newborn		
1. Anhaemopoietic	1. Anaemia of prematurity ...	3	1
2. Haemolytic	2. Acute haemolytic anaemia	5	0
Physiological jaundice	Icterus gravis neonatorum		
	1. Subacute	7	3
	2. Acute	7	4

In addition to the 5 cases of haemorrhage of the newborn there were 7 others of less severity which responded to the intramuscular injection of blood.

He points out that the underlying cause of the bleeding is a deficiency of prothrombin in the infant's plasma. There is reason to believe that prothrombin is formed in the placenta before birth and in the liver after birth. The liver just after birth is handicapped by a shortage of vitamin K and a functional insufficiency on the part of the liver itself. It would appear that the infant's liver after an interval can manufacture prothrombin from maternal vitamin K which it has received from its mother before birth in the absence of any further supply. In connexion with haemorrhagic disease of the newborn he considers the cardinal point to be that there is always more blood in the lumen of the gut than one can see on the napkin. For this reason death may come very quickly after the first appearance of external bleeding.

There are three methods of checking the bleeding. (1) By the administration of vitamin K, (2) intramuscular injection of blood, and (3) blood-transfusion.

If a sufficient quantity of vitamin K were given to all mothers before delivery it is probable that all babies would be born with a sufficient supply of prothrombin and haemorrhagic disease would not occur. Vitamin K administered after bleeding has started takes up several hours before it can be utilised by the liver and, therefore, except in very mild cases is too slow to be of any use.

The injection of whole blood in doses of 10 to 20 c.c. intramuscularly is a most useful procedure in all cases except the most severe. Injection should be repeated in three hours after the first dose. With intramuscular injection some interval of time has to elapse before prothrombin is absorbed from the injected blood and in severe cases the infant may die in this interval. In very severe cases the only possible effective treatment is by blood-transfusion. This provides prothrombin which can be immediately utilized and in addition blood-corpuscles and plasma to replace that which was lost.

The good results of blood-transfusion are most dramatic and delay in its use mostly results from want of appreciation of the severity of the condition.

Anaemia of prematurity is a common condition especially in infants weighing less than 3½ pounds at birth. The different factors contributing to this anaemia are that haemolysis shortly after birth tends to be greater in premature babies than in those born at term, they have a defective supply of iron and copper stored up at birth and their haemopoietic system is incapable of keeping pace with the infant's requirements. In mild cases the administration of iron, copper and liver extract is useful but in severe cases the only really effective treatment is blood-transfusion.

In acute haemolytic anaemia the cause of the condition is not clear. There appears to be a primary autogenous haemolysis. Transfusion in single doses in mild cases and repeated in the more severe not only replaces the lost blood cells but also inhibits the destructive process.

In jaundice of the newborn the physiological condition must be distinguished from icterus gravis neonatorum. The infant with physiological jaundice is red and yellow in colour. The cause of this condition is an inability on the part of the liver to deal with an excess of bilirubin, that is a mild condition of hepatic insufficiency.

When, in addition to being jaundiced, the infant is listless and drowsy, cannot be roused to feed and vomits if forcibly fed, there is an enlargement of the liver and spleen with haemorrhagic spots on the skin, the condition is one of icterus gravis associated with acute hepatic insufficiency.

Blood-transfusion is the only treatment leading to any success in cases of icterus gravis neonatorum.

It should be emphasized that haemolysis and liver damage are two separate pathological processes which may coexist in one infant, thus confusing the picture and not always giving a clear-cut diagnosis.

While jaundice does not necessarily accompany haemorrhagic disease of the newborn it is not surprising to find that in icterus gravis there is such severe hepatic damage that the formation of prothrombin is interfered with, and haemorrhage of severe degree may result.

The reason for the good results of blood-transfusion is not known, but it should be pointed out that transfusion is indicated in showing the classical signs of the condition even if there is a high haemoglobin value present.

R. H. B. ADAMSON.